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CHEMOSELECTIVE AND STEREOSELECTIVE EXPLORATION OF THE CHEMICAL REACTIVITY SPACE OF CASTAGNOLI-CUSHMAN-DERIVED ALLYLIC LACTAMOYL ESTERS: APPLICATION TO THE SYNTHESIS OF AZA-POLYCYLIC ARCHITECTURES

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Master of Science

Chemistry

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by

Brandon Joseph Mansker

June 2017

CENTRAL WASHINGTON UNIVERSITY

Graduate Studies

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Dean of Graduate Studies

ABSTRACT

CHEMOSELECTIVE AND STEREOSELECTIVE EXPLORATION OF THE CHEMICAL REACTIVITY SPACE OF CASTAGNOLI-CUSHMAN-DERIVED ALLYLIC LACTAMOYL ESTERS: APPLICATION TO THE SYNTHESIS OF AZA-POLYCYLIC ARCHITECTURES

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The synthesis and evaluation of structure-activity relationships of saturated nitrogen heterocycles is the focal point of various pharmaceutical companies thanks to the high biological activity of previously isolated azacycles. Here, we describe an operationally simple and highly efficient approach to macrocyclic lactams bearing vicinal stereocenters and a challenging cycloalkyne motif. The outcomes are achieved through a novel [4 + 2] cycloaddition reaction between an *N*-iodoarylated-1,3-azadiene and cyclic anhydrides, followed by interception of the cycloadducts in cross-coupling manifolds (*e.g.*, Sonogashira coupling) and concomitant lithiation-cyclization of the tethered alkyne. An unprecedented example of a hydroamino alkylation that is transition metal-free and occurs at room temperature will also be discussed.

ACKNOWLEDGEMENTS

In my five years here at Central Washington University, I have had the privilege of working with so many wonderful colleagues, faculty, and staff in and out of the Chemistry department. From challenging and interesting classes to long intense labs, collaborating with all of you has helped me grow personally and academically.

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Big thanks to all of my research group for helping me with reactions, keeping me smiling, and challenging me to do better in the lab. I would like to especially thank Spencer Langevin for the many years working together and always challenging me to do the best I can. Thank you Monique Khim for all of your help in keeping me organized and clear headed even in the most stressful of times. Thank you to all of my family and friends for all of your support throughout all of my academic career.

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CHAPTER 1

INTRODUCTION

Regio- and stereoselective functionalization of molecules are two of the most important challenges facing the modern synthetic organic chemist. Stereoselectivity is critical to the pharmaceutical industry since most drugs are chiral and must be produced in enantiopure or diastereopure form for FDA evaluation.[1-4] Minor stereoselective and structural modifications have been shown to have a major effect on the biological activity of existing pharmaceuticals. For example, Adderall and methamphetamine (Figure 1-1) are very similar in structure with the only difference being the appendage of a methyl group on nitrogen, which converts the primary amine resident in Adderall to the secondary amine present in methamphetamine.

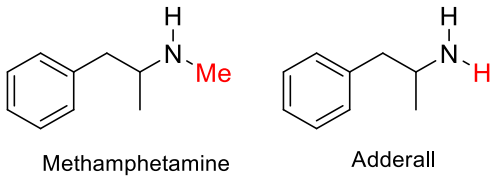


Figure 1-1. Chemical structures of methamphetamine and Adderall.

The addition of a methyl group allows for methamphetamine to cross the blood brain barrier faster than Adderall, leading to a higher potency.[5, 6] While Adderall can be addictive, it is used in the treatment of ADHD and narcolepsy due to its stimulating effect.[7-18] Methamphetamine, on the other hand, has no use in treatments and is used solely for the euphoric high.[5, 6, 19-34]

Accordingly, when designing a synthesis, modularity and flexibility need to be taken into account. Mechanistic understanding of developing methodology is necessary to advancing the field through rational design of substrates and reagents.

1.1: Diversity-oriented synthesis (DOS) of *N*-, *N,O*- *N,S*-, and *N,N*- heterocycles

Primarily due to the continuous search for new therapeutic agents for current difficult-to-cure diseases, the assembly of libraries of nitrogen-containing drug-like cyclic molecules with high quality, diversity, and enhanced potency has become a responsibility entrusted on synthetic organic chemists. Accordingly, the diversity-oriented synthesis (DOS) strategy, which aims to populate new chemical space with drug-like compounds that contain a high degree of molecular diversity, has emerged as an essential tool in chemical biology and drug discovery programs. However, designing *flexible, efficient, cost-effective* and *modular* strategies for accessing azaheterocyclic architectures can be quite daunting, in part due to conformational constraints and the proneness of some of the *N*-heterocycles to ring-opening. Nevertheless, the biological relevance of *N*-, *N,O*- and *N,S*-heterocycles (see chapter 2-1), as well as their architectural complexity, endear them to the medicinal and synthesis communities, thus, inspiring the development of increasingly more flexible, cutting-edge, time-honored, environmentally benign and cost-effective strategies for their construction, peripheral functionalization, and evaluation of structure-activity relationships (*i.e.*, SAR).[35] For example, as shown in Fig. 1-2, some of the frequently employed DOS tactics include those developed or popularized by aficionados such as Bode[36-40] (using SnAP and SLAP reagents), Cossy[41, 42] (using a ring expansion tactic), Bosch[43] (using bicyclic lactams), Charette[44] (using pyridinium salts),

Comins[45, 46]/Georg[47, 48] (using dihydropyridones), Liebeskind[49] (using organometallic scaffolding), Beak[50, 51]/Gawley[52-56]/O'Brien[57, 58]/Coldham[59, 60]/Meyers[61]/Clayden[62]/Beng[63-65] (using directed lithiation/ trapping protocols), and MacMillan[66-69] (using photoredox catalysis). These methods are discussed in detail below.

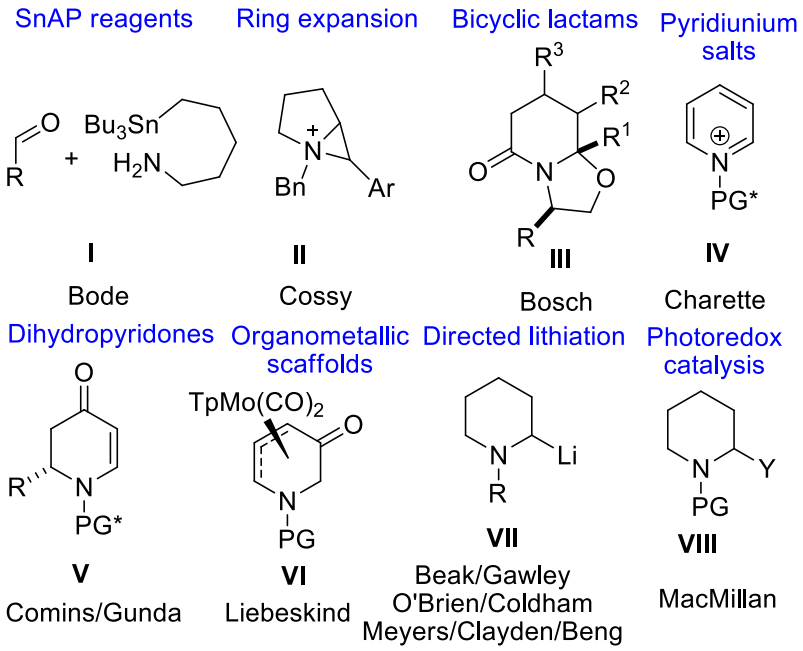
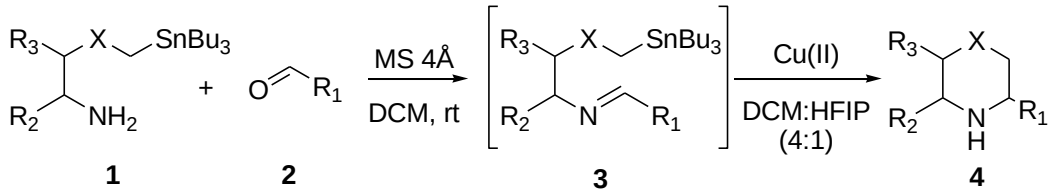


Figure 1-2. Examples of existing DOS tactics.

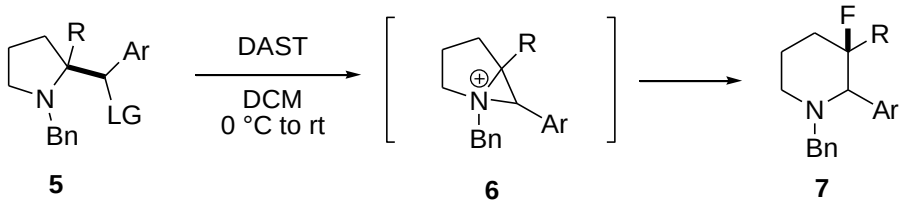
Access to substituted, *N*-unprotected heterocycles **4** through tin amine protocol (SnAP) reagents **1** reacting with an aldehyde **2** via imine intermediate **3** (Scheme 1-1).[70-73] Many SnAP reagents are commercially available due to the work of the Bode group parented with chemical manufactures. Custom SnAP reagents can be prepared using simple reagents and can range in functionality. The library of SnAP reagents allows for convenient, cost-effective, and modular synthesis of bicyclic and spirocyclic saturated *N*-heterocycles with varying ring size.[70] Other variations of SnAP reagents have been

investigated for their utility in expanding the diversity of *N*-heterocycle formations (i.e. HARP[74], SLAP[75, 76]).



Scheme 1-1. Access to α-substituted piperazine and other saturated N-heterocycles through reaction of SnAP reagent with aldehyde.

Biologically active compounds contain various sized heterocycles and the ability to expand or contract rings is useful in synthetic applications. The Cossy Group works on the ring expansion of leaving-group bearing pyrrolidines **5** to access 2,3,3-trisubstituted piperidines **7** through an intermediate aziridinium ion **6**, which exists as a tight ion pair (Scheme 1-2).[77-79] In recent years, fluorinated piperidines have been synthesized by opening of the transient aziridinium species with fluoride nucleophiles such as diethylaminosulfur trifluoride (DAST).[80] Obvious limitations of the Cossy methodology include the inability to utilize secondary amines and *N*-acyl amines. Additionally, tertiary pyrrolidinols are not tolerated since they instead undergo elimination under the reaction conditions.

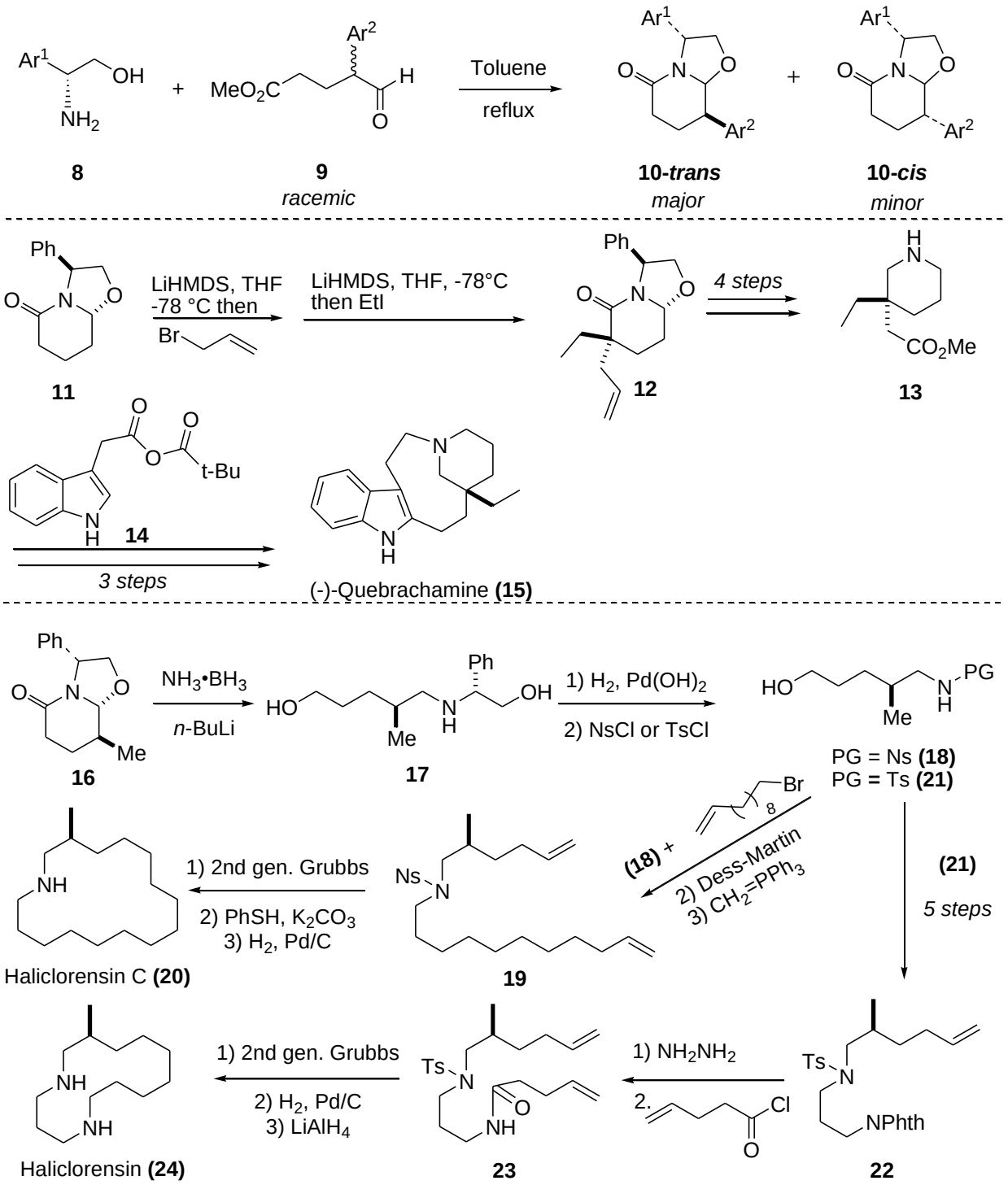


Scheme 1-2. Ring expansion of pyrrolidine derivatives to produce 2, 3, 3-trisubstituted piperidines.

In Bosch's synthesis of bicyclic δ-lactams through dynamic kinetic resolution of racemic γ-aryl-δ-oxoesters **9** with (*R*) - or (*S*)-phenylglycinol **8**,[81] it was found that cyclodehydration gave

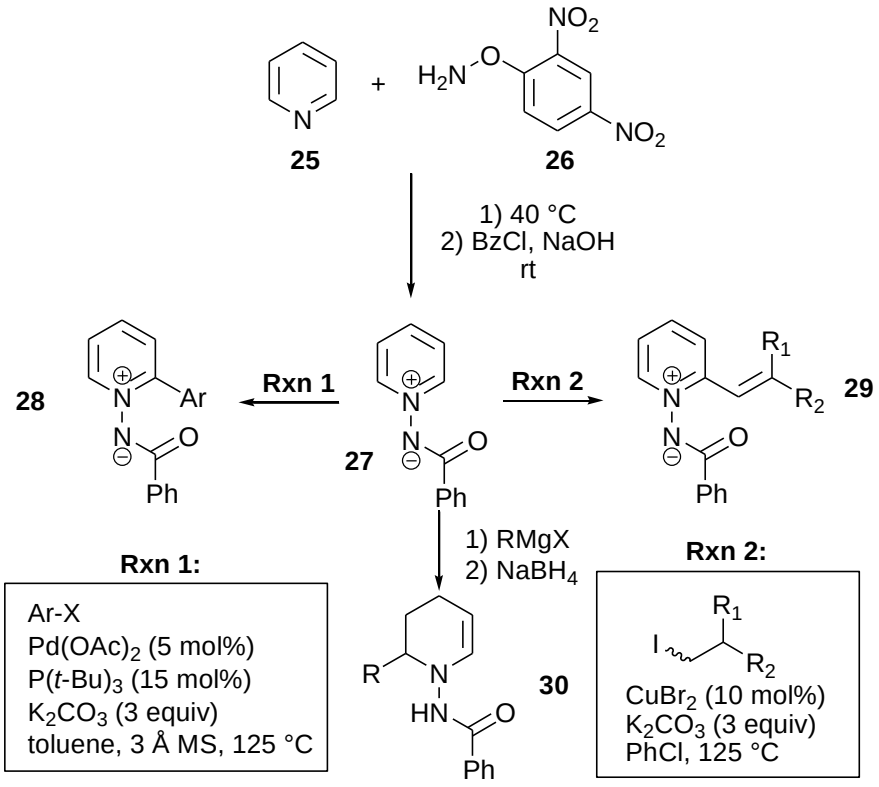
trans-3,8-aryl lactams **10-*trans*** as the major diastereomer (Scheme 1-3). Dynamic kinetic resolution established that the diastereomeric imines are at equilibrium with four oxazolidines with stereogenic centers.[82] Through the chair like six-membered lactams, isomeric oxazolidines produce the racemic bicyclic lactams. Bosch's intermediate has been further utilized to access functionalized heterocycles and macrocycles.[83-85] Through subsequent alkylation of *trans*-bicyclic lactams **11**, an isomeric 6-disubstituted bicyclic lactam **12** in the approach to (-)-Quebrachamine **15**, an indole alkaloid.[86].

Another synthetic application of the Bosch synthon is the synthesis of Haliclona alkaloids whereby an aza-macrocyclic ring is constructed (Scheme 1-3).[87] The reductive opening of δ-bicyclic lactam **16** followed by hydrogenolysis and protection affords an *N*-protected 4-methyl-5-aminopentanol **18, 21**. The subsequent synthesis of haliclorensin C uses a nosyl protecting group and subsequent alkylation, Dess-Martin oxidation, and Wittig olefination furnish two terminal alkene tethers **19**. The terminal alkenes then undergo olefin metathesis using Grubbs' second generation catalyst. Further deprotection and reduction afford haliclorensin C **20**. Haliclorensin synthesis uses a tosyl protecting group that undergoes a series of reactions to produce a phthalimido group **22**. This group will undergo hydrazinolysis followed by acylation to afford two terminal alkene tethers **23**. These tethers will be used with a 2nd generation Grubbs catalyst followed by a two part reduction to produce haliclorensin **24**.



Scheme 1-3. Bosch DOS approach to bicyclic lactams and its synthetic utility.

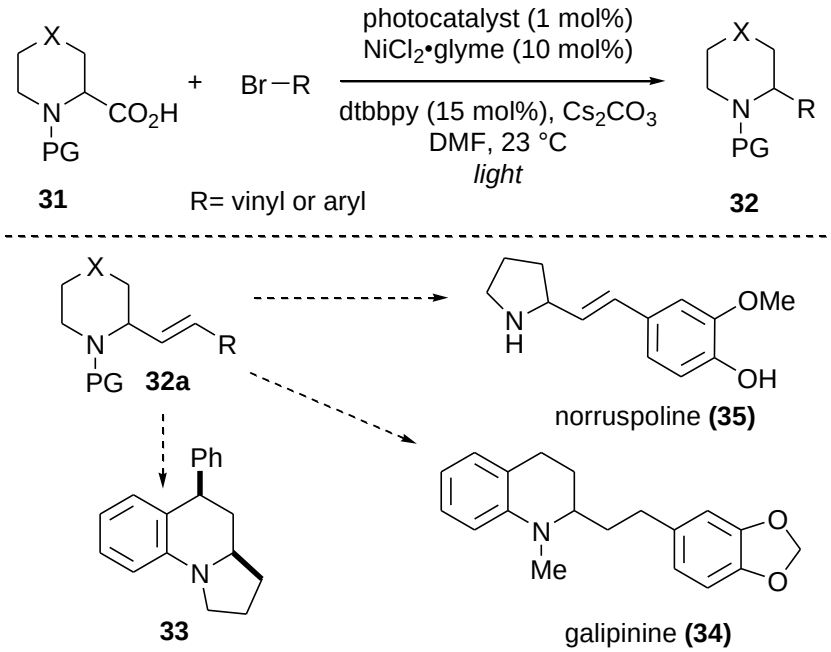
Charette utilizes an *N*-iminopyridiniums **27** to direct the addition of aryl **28** and alkenyl **29** Grignard reagents via intermediate bonding of magnesium to the carbonyl of the protecting group. The formation of *N*-iminopyridiniums and applications are depicted in Scheme 1-4.[88-93]



Scheme 1-4. Synthesis of *N*-iminopyridinium and applications to various functionalizations. The conditions for reaction 1 and reaction 2 are in the boxes below the compound.

Photoredox catalysis harnesses the energy of light to speed up a reaction through single-electron transfer, which is used to react compounds that are slow or unreactive. David MacMillan and co-workers merge photoredox with metal catalysis to achieve α-vinylation and α-arylation of a cyclic amino acid.[94] Photoredox is used due to the α-CH bond being inactivated thus allowing photoredox to activate it. Catalytic amounts of photocatalyst and nickel complex with ligand were added to an amino acid **31** to produce α-substituted amine **32** as seen in Scheme 1-5.[95] This showcases a new way of sp^3-sp^2 coupling in the inactivated α position of heterocyclic

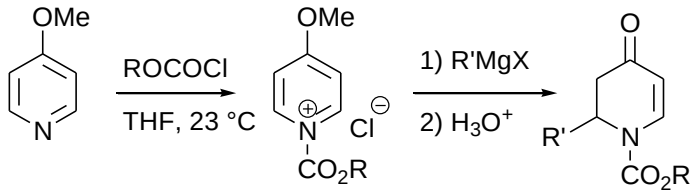
rings. This new discovery led to easier access to natural products and pharmaceuticals via the substituted group. Cyclic enamine **32a** is used to form bicycles **33** or natural products **34** and **35** as seen in Scheme 1-5.[96]



Scheme 1-5. Photoredox-metal catalysis of cyclic amino acid to afford α-substituted amine and application of cyclic enamine.

Direct sp^3-sp^2 coupling can be applied to assemble a library of compounds including heterocycles, thus, providing an effective approach for functionalizing unactivated C-H bonds.

Dihydropyridones are doubly saturated pyridones and are used as a synthetic building block for various synthetic pathways. The synthesis of dihydropyridone **38** begins with 4-methoxypyridine **36** reacting with aryl chloroformate followed by Grignard addition and subsequent acidic workup in Scheme 1-6.[97]



Scheme 1-6. Synthesis of dihydropyridones through 4-methoxypyridine. R groups are aryl, methyl, and alkyl groups.

Since the Comins' synthetic approach to dihydropyridones in the early 1980s, many advancements, applications, and adaptations of dihydropyridones have been discovered.[97-107] Attributable to the different functional positions in the dihydropyridones, the synthetic applications are expansive and diverse. A few of the possible synthetic transformations can be seen in Figure 1-3.[108]

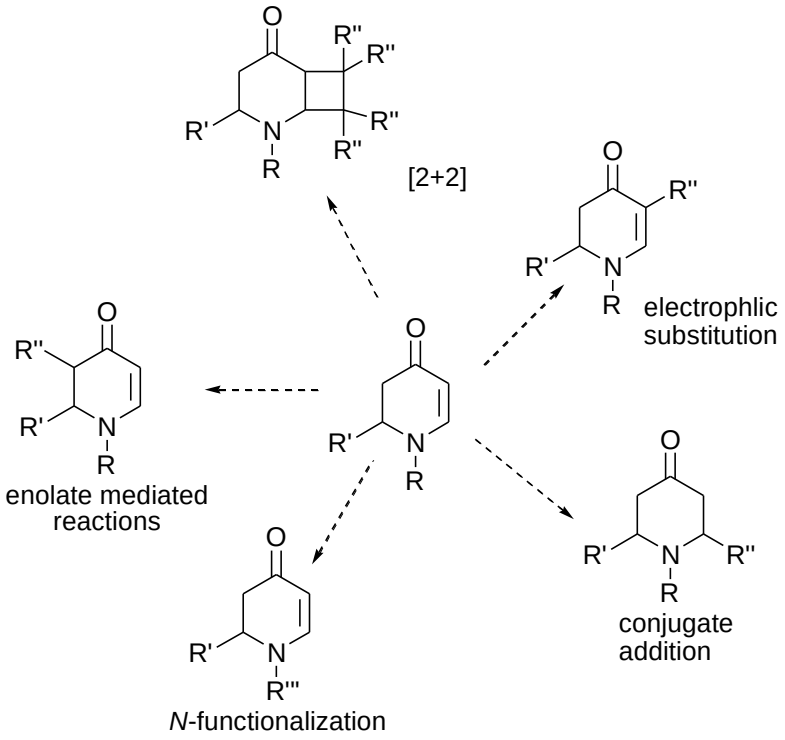
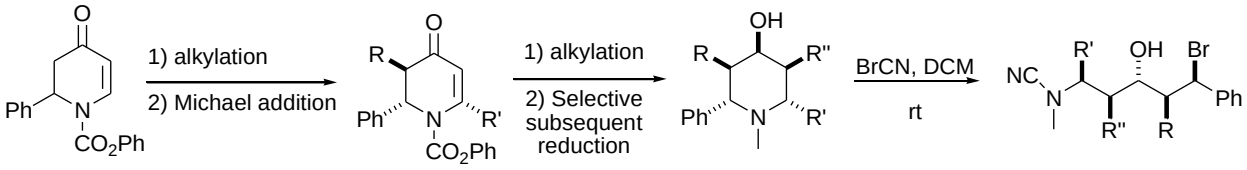


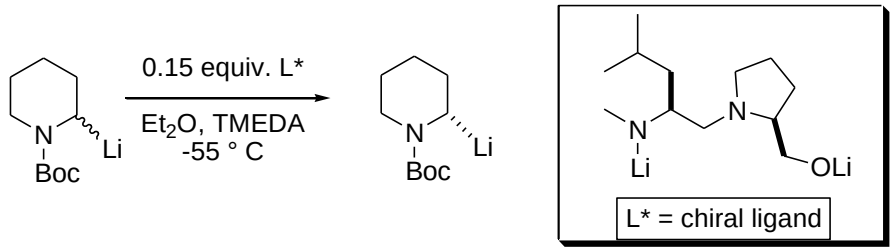
Figure 1-3. Synthetic transformations of dihydropyridones. Many other transformations can be achieved, the ones presented offer a diverse group of reactions.

The use of amino acids and amino ynone has enabled functionalization in all positions and established stereocontrol for the creation of multiple chiral centers. Complete functionalization gives a multi-substituted piperidone that can ring open accessing regio- and stereoselective alkylamine derivatives with cyanogen bromide.[109] Overview of this synthesis is depicted in Scheme 1-7.



Scheme 1-7. Synthesis of highly functionalized alkylamines through dihydropyridones. Regio- and stereoselectivity of the final product is controlled and contained five stereocenters.

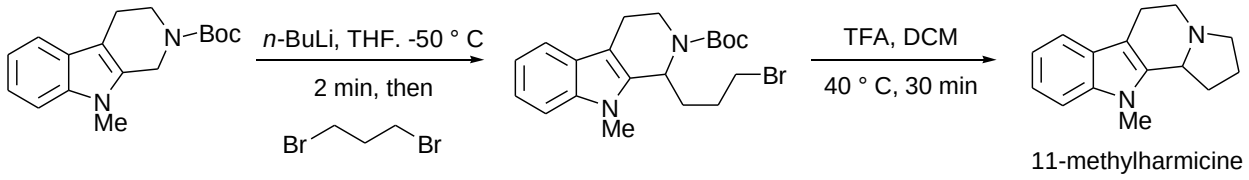
Organolithium compounds are used in organic synthesis for multiple purposes. Conventional lithiation reactions can append a lithium α-amino of an *N*-protected piperidine, however, a racemic mixture is achieved. Through the use of dynamic thermodynamic resolution (DTR), a chiral ligand can resolve the racemic organolithium intermediate as seen in Scheme 1-8.[110]



Scheme 1-8. Catalytic resolution of 2-lithio-N-Boc-piperidine with a chiral ligand. DTR, temperature control, and varying concentrations of reagents were used to find the best conditions.

Directed lithiation has been utilized in the synthesis of functionalized heterocycles and bicycles found in natural products and pharmaceuticals. Due to the proximity of the lithium to the heteroatom, fused heterocycles are easily accessible. An example can be seen in Scheme 1-9

with the synthesis of a modified harmicine, a tetrahydro-β-carboline, through directed lithiation of a tetrahydro-2-Boc-pyridindole compound followed by cyclization.[111]



Scheme 1-9. Synthetic approach to 11-methylharmicine via tetrahydro-2-Boc-pyridindole. Due to effects of N-substituents, methyl was the only suitable substituent to undergo further reactions.

Other researchers have worked on directed lithiation of heterocyclic motifs and advancements are still being made in lithium chemistry.[54, 112-123] Uses for lithiation chemistry are expansive and diverse due to the reactivity of lithium.

1.2: Relevance of functionalized lactams

Lactams are cyclic amides of various ring sizes such as alpha (α), beta (β), gamma (γ), and delta (δ) depicted in Figure 1-4.

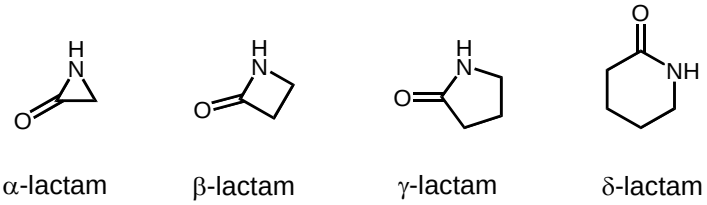


Figure 1-4. Various sized lactams. Alpha (3 membered rings), beta (4 membered rings), gamma (5 membered rings), and delta (6 membered rings).

Lactams differ from acyclic amides due to resonance between the nitrogen atoms lone pair and the carbonyl, thus, imposing planarity. Changing the size of ring affects the stability and strain of each of the lactams. The β-lactam is one of the most studied heterocycles in the last

century due to the impact on antibiotics and other biological activities. Examples of antibiotics and pharmaceuticals containing a β-lactam are displayed in Figure 1-5.

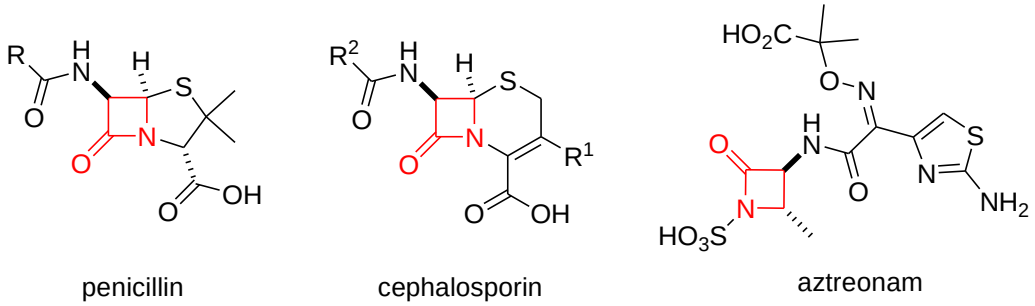


Figure 1-5. Examples of biologically active β-lactams.

Penicillin was one of the first medications to treat bacterial infections (1928) and still is widely used to treat infections, but due to bacteria developing resistance, penicillin is not able to treat many bacterial infections. Cephalosporin is a class of antibiotics used in preventive medicine and treating various bacterial infections (there are five generations of this antibiotic). Aztreonam is a monolactam antibiotic used to treat infections caused by cystic fibrosis and was approved by FDA in 1986. In natural product isolation, δ-lactams and γ-lactams have been isolated from plants and tend to be highly functionalized. Examples of δ-lactams and γ-lactams discovered through natural products are seen in Figure 1-6. The prevalence of highly substituted lactams in natural products with biological activation potential has led to an increase in research on the synthesis of similar lactams. Functionalizing positions of a lactam can be done by hindering attack on the carbonyl side directing C-C bond formation to α or β and the carbonyl of the lactam can undergo reactions to further functionalize the cyclic amide.

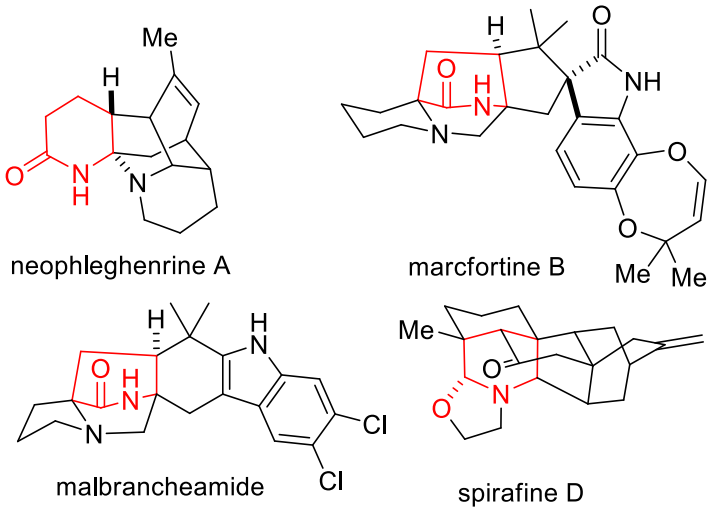
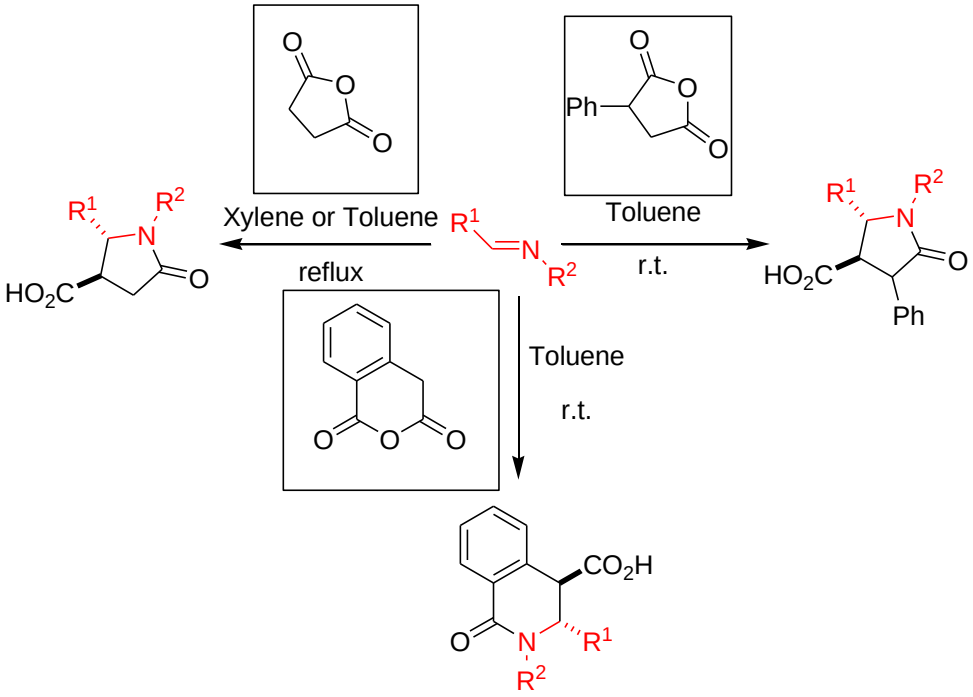


Figure 1-6. Delta-lactams found in natural products.

Neophleghenrine A was isolated from Phlegmariurus henyri containing a 9-azaprotoadamantane core and belong to a family of bioactive alkaloids. Marcfortine B is an indolic secondary metabolite with a substituted spirocyclic δ-lactam and γ-lactam. Malbrancheamide contains a [2, 2, 2]-diazabicyclic core which is found in diverse biological compounds containing the same substituted spirocycle as marcfortine B. Spiradine D was isolated from Spiraea japonica L which features an oxazolidine utilizing the carbonyl of the lactam.

1.3: The Castagnoli-Cushman Reaction (CCR): Current state of affairs

Reaction of anhydrides with imines has provided access to *trans*-configured lactams through the Castagnoli-Cushman reaction.[124] Castagnoli began with simple alicyclic anhydrides at elevated temperatures. Later, Cushman expanded the anhydride scope to highly reactive anhydrides such as homophthalic anhydride and 2-phenylsuccinic anhydride in Scheme 1-10.[125]

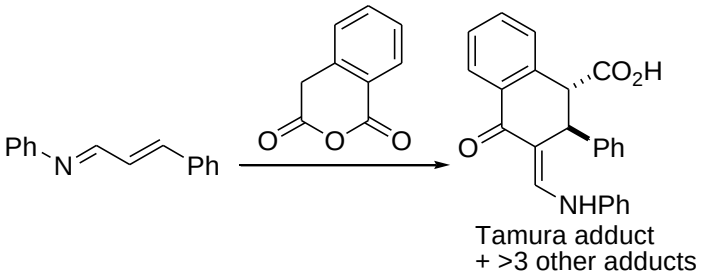


Scheme 1-10. CCR substrate and conditions from 1969 by Castagnoli and expansion by Cushman. Alicyclic anhydride (1), homophthalic anhydride (2), and 3-phenylsuccinic anhydride react with imine to afford substituted lactamoyl acids.

1.4: Challenges associated with CCR methodology

We are aware that the use of 1,3-azadienes with homophthalic anhydride reacts to form many adducts. Tamura adducts are the most abundant, which is when the reaction takes place on

the alkene and not the imine. Scheme 1-10 shows the findings from Haimova that homophthalic anhydride reacts with 1,3-azadienes to form mostly Tamura adducts.[126]



Scheme 1-11. Annulation of homophthalic anhydride with 1, 3-azadienes to form Tamura and other adducts.

Therefore, the alkene is in competition with the imine when undergoing reactions with anhydrides. Due to the promiscuous nature of the 1,3-azadienes, they were deemed synthetically unattractive as no heterocycle was formed in the process.

With knowledge of previous research on common intermediates, we propose our own common intermediate that can be seen in Figure 1-7.

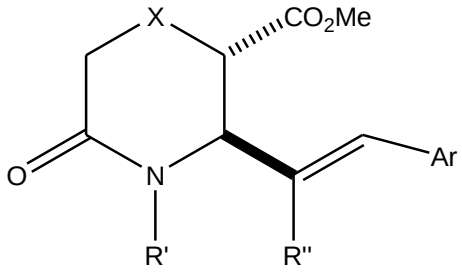


Figure 1-7. Our common intermediate, allylic lactamoyl ester.

This intermediate will allow functionalization in every position of an *N*-heterocycle through appending three different functional groups during formation. Synthesis and utility of this common intermediate will be discussed in detail further in this thesis.

CHAPTER 2

DIVERSITY-ORIENTED SYNTHESIS OF VICINALLY FUNCTIONALIZED ALLYLIC LACTAMOYL ESTERS USING THE CASTAGNOLI-CUSHMAN REACTION

2.1: Relevance of *N*-, *N*, *O*- *N*, *S*-, and *N*, *N*- heterocycles

The synthesis and evaluation of structure-activity relationships of saturated nitrogen heterocycles are the focal points of various pharmaceutical companies owing to the high biological activity of previously isolated azacycles. *N*-heterocycles are highly prevalent in natural products, thus ideal candidates for functionalization through the synthesis of similar structures. Selected examples of bioactive *N*-heterocycles are depicted in Figure 2-1.

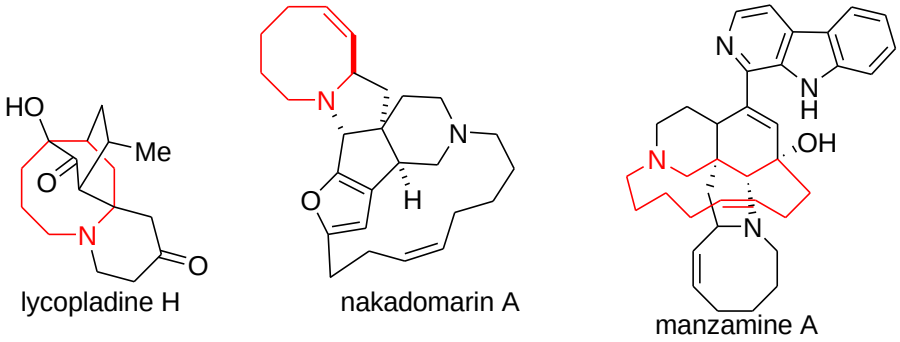


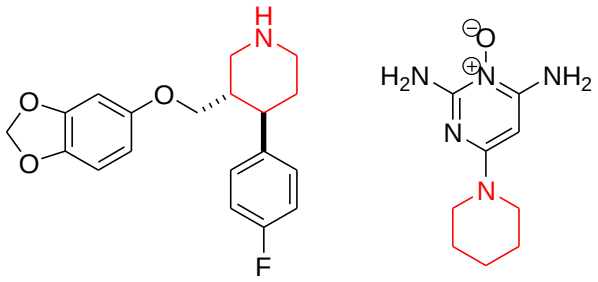
Figure 2-1. Bioactive N-heterocycles. Fittingly, the synthesis and further elaboration of N-heterocyclic motifs are being explored by many research groups, including but not limited to those employed by aficionados such as Bosch, MacMillan, Comins, Gunda, Beak, Gawley, O'Brien, Coldham, Beng, Clayden, Cossy and Charette.

Lycopladine H was isolated from the club moss *Lycopodium complanatum* and belongs to a family of novel *Lycopodium* alkaloids. This tetracyclic metabolite exhibits several novel architectural features, including an azacyclooctane and a spiro-fused 3-piperidone.[127] Due to

these features, the synthesis of lycopladine H has proven to be difficult in achieving the formation of the complex tetracyclic scaffold. Nakadomarin A is a marine alkaloid of the manzamine family containing two bridged *N*-bicycles. Comprised of an unprecedented 8/5/5/5/15/6 ring system, nakadomarin A has been isolated from an Okinawan marine sponge *Amphimedon* sp., by Kobayashi and co-workers in 1997.[128] Nakadomarin A exhibited a number of pharmaceutical applications: a cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL), inhibitor of cyclin-dependent kinase 4 (IC_{50} 9.9 μg/mL), antimicrobial towards *Trichophyton mentagrophytes* (MIC 23 μg/mL), and a Gram-positive bacterium (*Corynebacterium xerosis*, MIC 11 μg/mL).[129] Various synthetic methodologies towards nakadomarin A have been developed that focus on the synthesis of the core.[130-134] However, only one total synthesis of (-) has been discovered and two of its antipode.[135-137] Manzamine A[114, 115, 117, 118, 120, 138-153] is a marine alkaloid of the manzamine family and was isolated from a sponge in the Okinawan sea by Sakai and Higa in 1986. It exhibits a range of biological activities such as insecticidal, antibacterial, anti-inflammatory, and anti-cancer and anti-malarial.[16] Manzamine A contains a pentacyclic core with two *Z*-olefins, two tertiary amines at ring junctions, five stereocenters, and an attached β-carboline heteroaromatic tricyclic system. Similar to nakadomarin A, many papers describe the synthesis of the core but only four total syntheses have been reported by Winkler[154], Martin, Fukuyama[155], and Dixon.[156] These examples of biological active *N*-heterocycles given evidence that the synthesis of various *N*-heterocycles can lead to the development of new, better pharmaceuticals.

N-, N, O- N, S-, and N, N- heterocycles vary from a typical cyclic structure due to the effects on chemical properties with the introduction of a heteroatom into the ring system. The biological applications and structural complexity of these heterocycles inspire the development

of new synthetic and medicinal application through more efficient strategies of constructing and increasing functionality. Piperidines are nitrogen containing six-membered ring systems (*N*-heterocycles). They are widely used as a building block and chemical reagent for the synthesis of organic compounds with a secondary amine that can be functionalized and effect α,β-positions to induce reactivity. Substituted piperidines are widely used in pharmaceuticals due to the biological activity. Examples of biological active piperidines are depicted in Figure 2-2.



paroxetine minoxidil

Figure 2-2. Bioactive piperidines.

Paroxetine is a selective serotonin uptake inhibitor for the treatment of depression and Parkinson's disease. Minoxidil is an antihypertensive vasodilator medication for the treatment of hair loss. Morpholines are six-membered rings with a nitrogen and an ether oxygen in a 1, 4 configuration *(N, O*-heterocycles). The ether oxygen withdraws electron density from the nitrogen causing a decrease in nucleophilicity thus the synthesis of morpholines can be challenging due to their proneness to ring-opening, stereoselectivity, and economical approaches. Substituted morpholines have been isolated from natural products and synthesized with many displaying biological activity. Examples of biological active morpholines are represented in Figure 2-3.

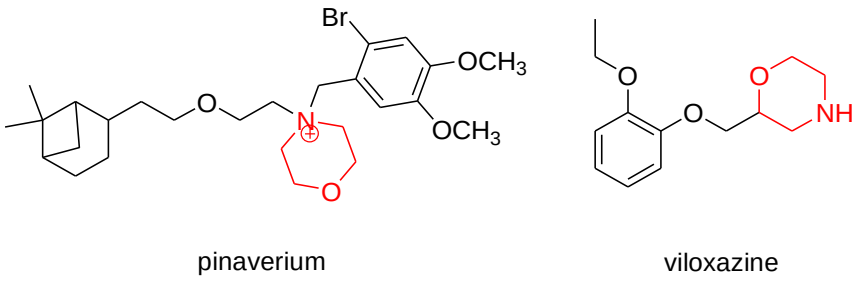


Figure 2-3. Bioactive morpholines.

Pinaverium is an antispasmodic and calcium channel blocker for the treatment of functional gastrointestinal disorders. Viloxazine is a selective norepinephrine reuptake inhibitor (NRI) used as an antidepressant. Thiomorpholines are six-member rings with a nitrogen and sulfur in a 1, 4 configuration *(N, S*-heterocycles). The properties of these thiomorpholines are similar to morpholines with an electron withdrawing effect by the sulfur on the nitrogen. Due to the withdrawing effect by the sulfur, the conformation will be pulled by the sulfur away from the nitrogen. Sulfur is multivalent but still relatively small in size so it can be useful for increasing reactivity. Thiomorpholines can be found in pharmaceutical drugs covering many different bioactivities and some examples can be seen in Figure 2-4.

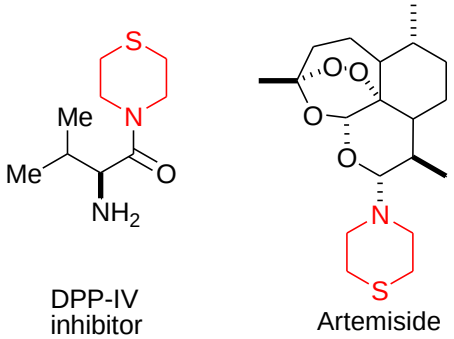


Figure 2-4. Thiomorpholines examples of bioactive compounds.

DPP-IV inhibitor treats type 2 diabetes (DPP-IV = dipeptidyl peptidase-4). Artemiside is used for the treatment of toxoplasmosis, a parasitic infection, which is common among

chemotherapy patients. Piperazines are six-membered rings containing two nitrogen atoms in a 1, 4-configuration (*N*, *N*-heterocycles). With the addition of another amine, the basicity of the structure will increase due to the lone pair of electrons. Functionalization of the nitrogen can lead to double functionalization with the option to place different substituents on each nitrogen. Piperazines are found widely in pharmaceuticals but some piperazines are illegal due to recreational use because euphoric and stimulant properties. Examples of piperazines in pharmaceutical drugs and illegal drugs are shown in Figure 2-5.

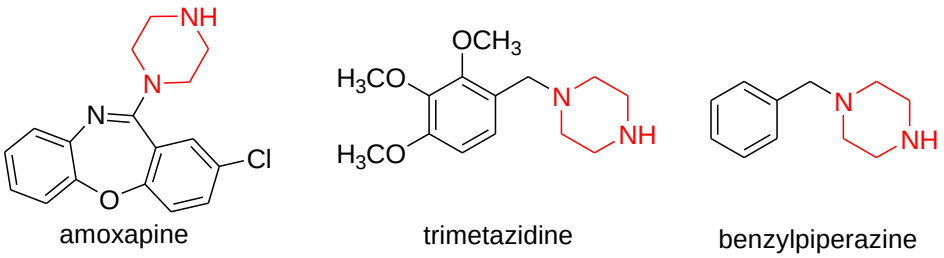


Figure 2-5. Piperazines found in pharmaceutical drugs and illegal drugs.

Amoxapine is a tetracyclic antidepressant (part of a large family of antidepressants) used in the treatment of major depressive disorders. Trimetazidine is used for the treatment of angina (chest pain) and as a cytoprotective anti-ischemic. Benzylpiperazine was synthesized as a potential anthelminthic for farm animals but went through clinical trials which determined that there was no use for it. However, in the early 1990s, it was found to be used recreationally in many parts of the country due to its euphoric and stimuli effects. *N*-heterocycles are utilized heavily in pharmaceuticals due to their biological activities. Synthesis of functionalized *N*-heterocycles have proven to be advantageous in discovering new pharmaceuticals thus research in this area is in high demand. Development of cost-effective, rapid, and modular synthesis of *N*-heterocycles will be discussed in this thesis.

Many of the *N*-heterocyclic pharmaceutical shown in Figure 2-2, 2-3, 2-4, and 2-5 only have *N*-substituents while leaving most of the ring unsubstituted. Synthetic approaches limit the ability to react with the other positions of the ring due to the high reactivity of the heteroatom. In the synthesis of these heterocyclic compounds, the heterocyclic portion is not synthesized but rather bought due to the complications in synthesizing clean heterocycles. Functionalizing other positions of the heterocycles can lead to advancements in pharmaceuticals and applications to other isolated compounds. Therefore, redesigning the synthesis of the heterocyclic core could lead to the ability to functionalize other positions in the ring.

2.2: Proposed plan for accessing allylic lactamoyl esters and their potential synthetic utility

As mentioned above, functionalized piperidines, morpholines, thiomorpholines, and piperazines constitute the core of several alkaloid natural products, natural or unnatural amino acids, ligands and pharmaceuticals.[157]

Circumscribed in these classes of azaheterocycles is a subset, which bears *vicinal stereocenters*. However, controlling the formation of (labile) vicinal stereocenters on the skeleton of a piperidine, piperazine or (thio)morpholine poses a considerable challenge, in part because sequential substitution of a 2- or 3-substituted cyclic amine derivative is only marginally tolerated in most of the existing C-2 or C-3 functionalization strategies. Along these lines, our group previously disclosed that the addition of alkyllithium nucleophiles to the β-position of α-arylated dehydropiperidines followed by interception of the intermediate tertiary organolithium with electrophiles furnishes polysubstituted benzylic piperidine derivatives in excellent diastereoselectivities (Figure 2-6A).[64, 65] Disappointingly, from the standpoint of generality,

dehydromorpholines tended to undergo undesirable ring opening. Perhaps more disheartening to date is our inability to extend the methodology to α-alkenyl enecarbamates as we are caught at the crossroads of alkene *vs* enecarbamate carbolithiation.

Desiring a *modular* approach to *vicinally* functionalized and potentially bioactive *N*-heterocycles bearing an *alkenyl motif* at the α-amino position, and seeking to side-step the aforementioned limitations, we became interested in investigating the fate of (hetero)cyclic anhydrides of type **3** in formal [4 + 2] cycloadditions with 1,3-azadienes such as **4** (Figure 2-6B, see **5**–**8**). We were fully aware of Haimova's previous findings that while homophthalic anhydride (**3h**) reacts efficiently with simple aromatic imines such as **9** to afford azaheterocyclic Castagnoli-type cycloadducts of type **10**,[126, 158] its reaction with α,β-unsaturated imines such as **4** proceeds through a plethora of reaction pathways, including Tamura-like[159-161] (see carbocyclic enaminone **11**, Figure 2-6C), Castagnoli-type and Perkin condensation-type[125] pathways. Indeed, the promiscuous nature of **4** has understandably led researchers to the somewhat hasty conclusion that its reaction with cyclic anhydrides is '*synthetically unattractive*'.[125] We therefore stoically embraced the challenge and surmised that the *decreased α-CH acidity* of anhydrides would serve to provide an ideal balance of reactivity and selectivity.

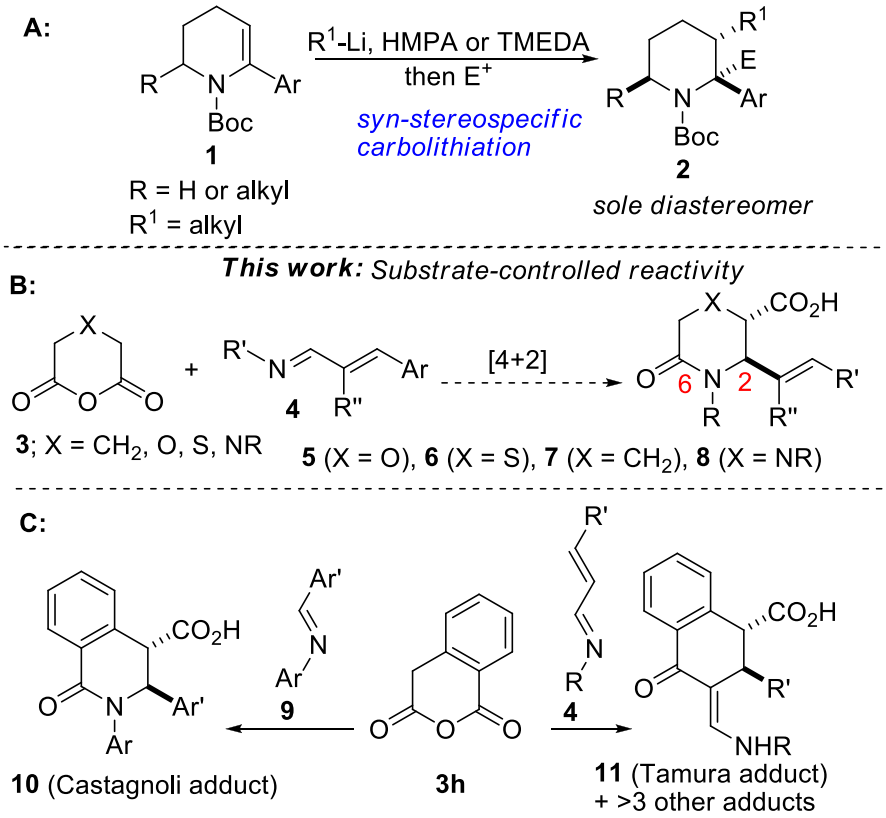


Figure 2-6. Previous and current work on vicinal functionalized heterocycles. (A) Vicinal functionalization of α-arylated dehydropiperidines by carbolithation-trapping[64, 65] (B) Proposed plan for accessing vicinally functionalized allylic morpholinones, thiomorpholinones and piperidinones (C) Annulation of homophthalic anhydride with 1,3-azadienes.[126, 158]

We reasoned that the appendage of an alkenyl motif on the skeleton of a nitrogen heterocycle would pave the way for harnessing several reactivity modes, including hydrogenation,[162] hydroarylation,[163] oxoamination,[164] metathesis,[165] or trifluoromethylation.[166] It was, however, recognized that successful implementation of the planned strategy would hinge on our ability to (i) achieve *substrate-controlled reactivity*, (ii) mitigate *E*/*Z* isomerization or double-bond migration, and (iii) achieve site-selective functionalization of **5**–**8**. Herein, detailed efforts are described.

2.3: Results and Discussion

We initiated studies on the construction of vicinally functionalized *allylic* lactamoyl acids/esters by assembling a diverse range of enolizable cyclic anhydrides and 1,3-azadienes (Figure 2-7, see **3a–h** and **4a–z**, respectively). Synthetic procedures for **3** and **4** are detailed in the experimental section.

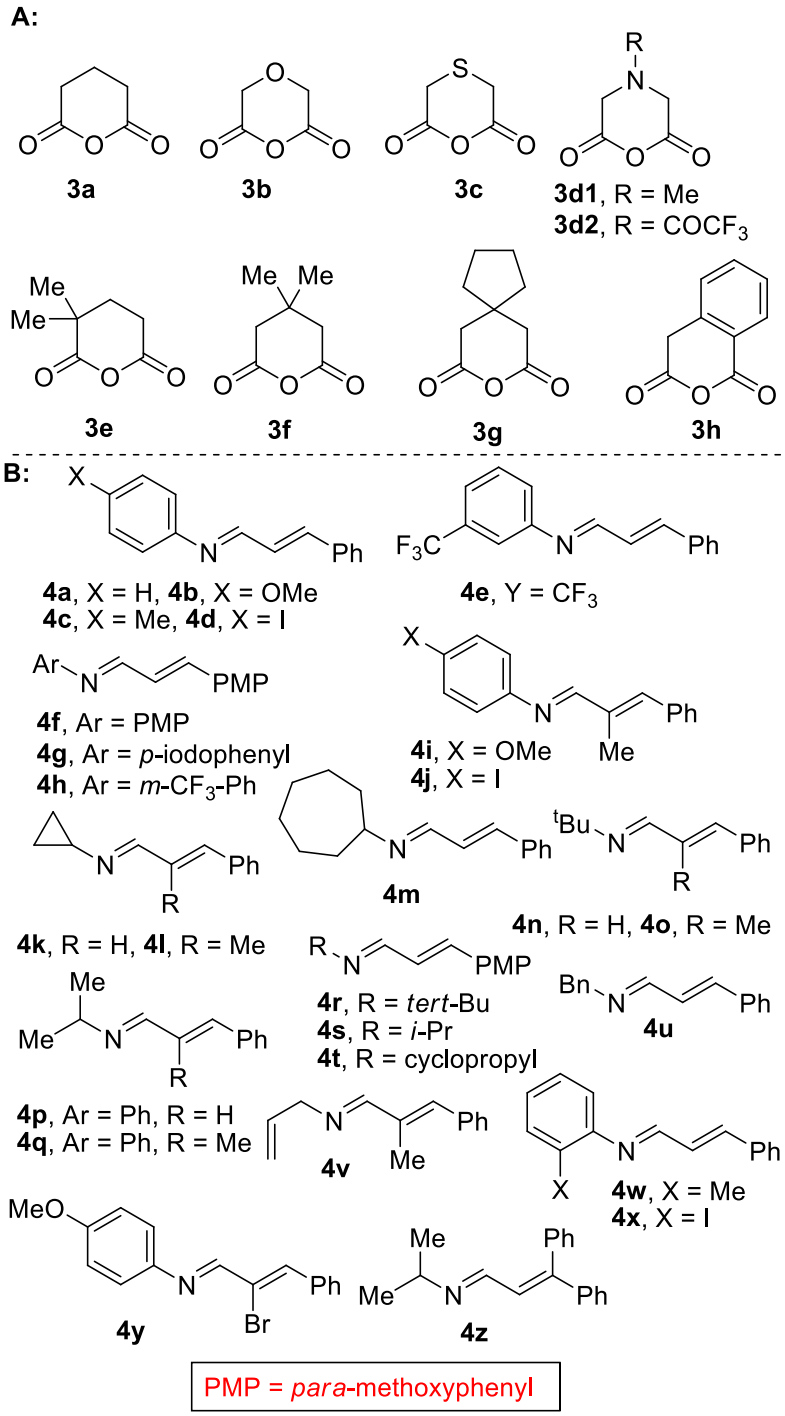


Figure 2-7. Examples of cyclic anhydrides (*i.e.*, **3**) and 1,3-azadienes (*i.e.*, **4**) employed in these studies.

2.3.1: Synthesis of allylic morpholinonates

Foremost among our objectives was to access allylic morpholinonates, which are somewhat difficult to synthesize due to the proneness of the morpholine heterocycle to ring opening. Gleaning from recent insightful reports (these appeared while this project was at the incipient stages) from the laboratories of Burdzhiev[167] and Krasavin[168] on the use of digylcolic anhydride (**3b**) in a Castagnoli-Cushman reaction with unconjugated imines, model azadiene **4a** and **3b** were engaged in a thermally induced [4 + 2] cycloaddition, using toluene as the solvent. Pleasingly, after stirring for 12 h at 90 ^{o}C, GC-MS and ^{1}H NMR analyses of the methylated crude mixture revealed the presence of a single cycloadduct (Scheme 2-1, see **5a2**). The exclusive and stereocontrolled formation of the *E*-configured styrene derivative **5a2** indicates a preference for a Castagnoli-Cushman-type reaction over a Tamura-like cycloaddition; the latter being the preferred pathway when homophthalic anhydride was employed (Figure 2-6C, see **11**).[126] Encouraged by this outcome, and after establishing that toluene out-performs other solvents (*e.g.*, EtOAc, 2-MeTHF and 1,4-dioxane), we next moved to evaluate the scope of the transformation with respect to the *N*-substituent and the alkenyl motif. We have found that electronically diverse imino dienes are well tolerated. For example, allylic lactam **5c2**, which bears an electron-donating *p*-methoxyphenyl (*i.e.*, PMP) group is affordable in impeccable yield and in excellent diastereoselectivity. This is a synthetically appealing result given that in addition to being readily removable (making it a place-holder for other *N*-substituents),[169] the PMP group is amenable to further functionalization under several reaction manifolds, including transition metal-catalyzed cross-couplings of the aryl ether subunit. The amenability of electron-poor 1,3-azadienes of type **4e** to this hexannulation protocol has set the stage for rapid installation of pharmaceutically relevant motifs such as a trifluoromethylaryl group (see **5d2**). *N*-aryl imino

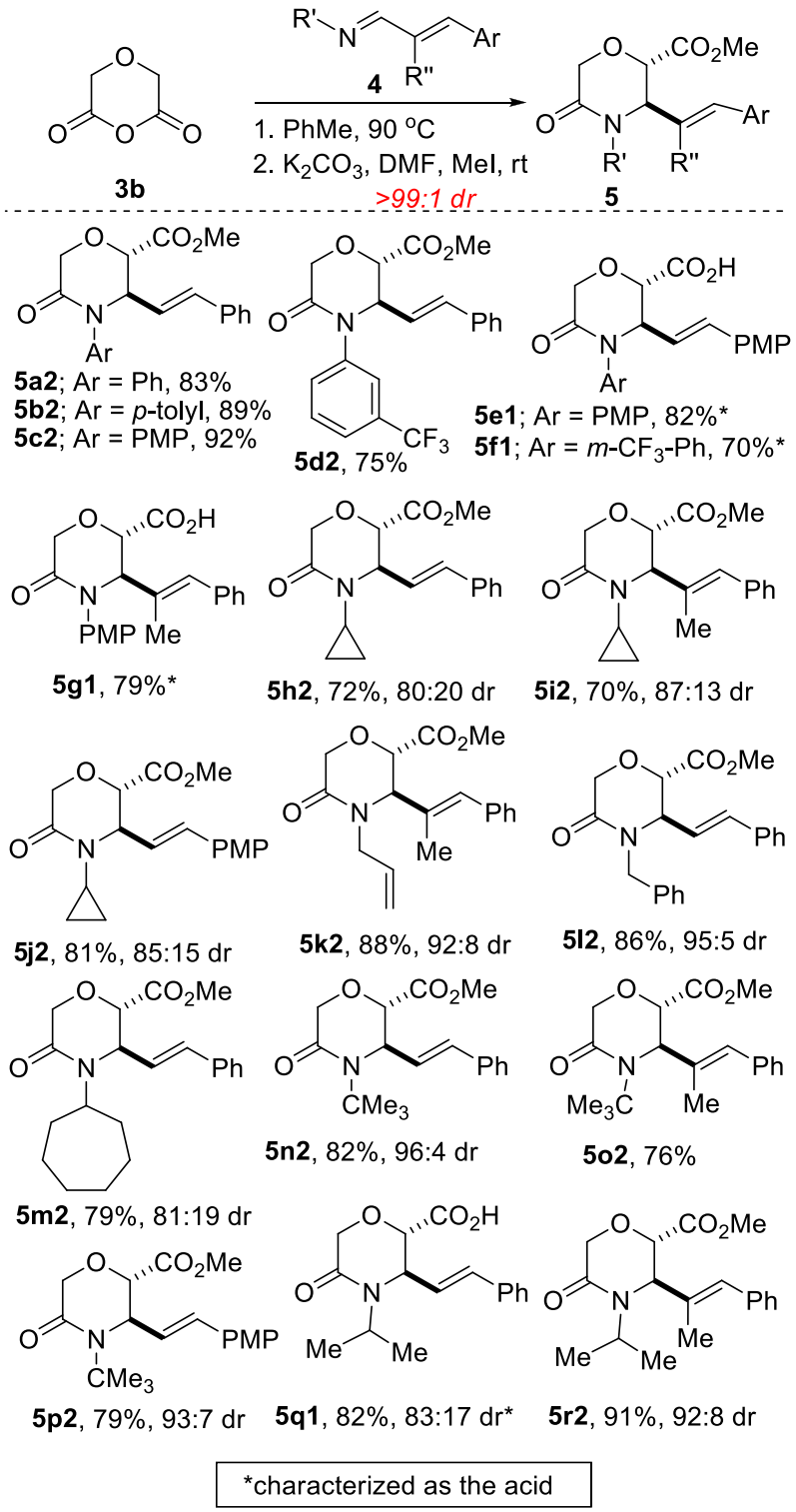
dienes derived from substituted cinnamaldehydes react stereoselectively with diglycolic anhydride (see **5e1** & **5f1**). Importantly, internally substituted *N*-aryl-1,3-azadienes seamlessly undergo productive hexannulation to afford cycloadducts such as **5g1**, without any complications arising from *E*/*Z* isomerization. This result further highlights the merits of our strategy given that *stereodefined* approaches to *trisubstituted styrene* derivatives are at a premium.[170-173]

Knowing that the nature of the *N*-substituent present on a morpholine ring can have a dramatic effect on its biological activity, the amenability of 1,3-azadienes bearing nonaryl *N*-substituents to substrate-controlled hexannulation with **3b**, was next explored. Encouragingly, cycloalkyl-, allyl-, benzyl-, isopropyl- and *tert*-butyl-containing imino dienes are all competent reactive partners (see **5h2–r2**).

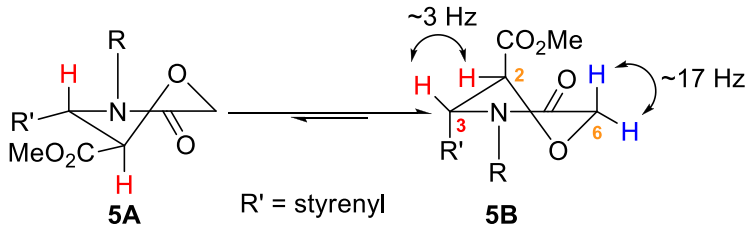
The relative configuration of the products depicted in Scheme 2-1 was assigned using coupling constant analysis (Figure 2-8), and also by analogy to those of the unambiguously established benzylic counterparts.[168]

2.3.2: Synthesis of thiomorpholinonates from thiodiglycolic anhydride **3c**

Thiomorpholines have similar properties to morpholines but vary due to the increase in size to sulfur from oxygen. The synthesis of thiomorpholine derivatives is even more challenging than that of morpholine derivatives due to the enhanced lability hence the increased proneness to ring opening. Discovering a selective and effective process for the synthesis of functionalized thiomorpholines would be a major advancement. Our studies have revealed that thiodiglycolic anhydride (**3c**), whose α-CH acidity is close to that of homophthalic anhydride (**3h**) displays unproductive reactivity with inherently more reactive *N*-benzylazadienes, even at 60 ^{o}C (Scheme 2-2, see **6a1**/**6a1'**). The crude mixture in this case showed evidence of formation of the Tamura adduct (*i.e.*, **6a1'**).

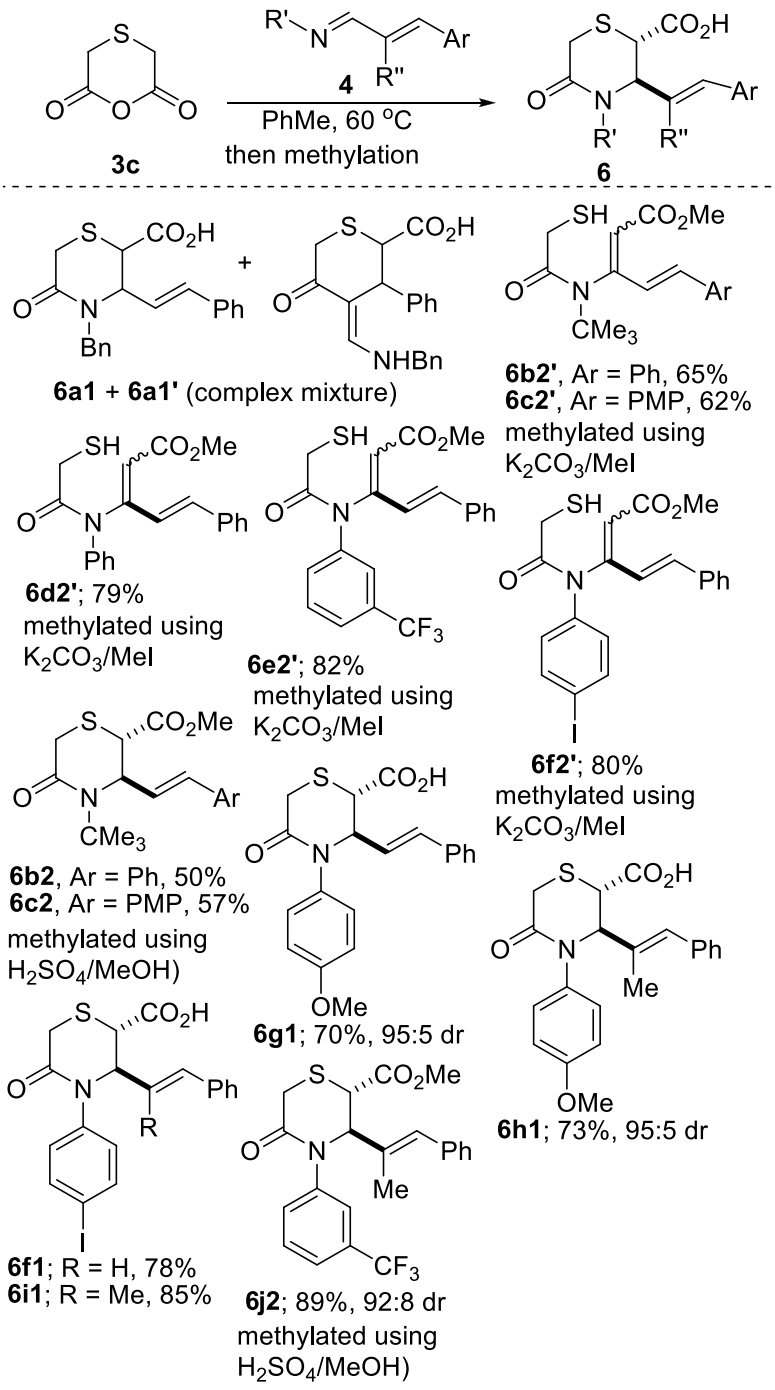


Scheme 2-1. Annulation of 1,3-azadienes with diglycolic anhydride **3b.**



Trans relative configuration supported by X-ray analysis
$^{3}J_{H2\text{-}H3}$ = 1.5 - 4.5 Hz (consistent with **5B**)
$^{2}J_{H6\text{-}H6}$ = 16.5 - 17.0 Hz (large geminal coupling constant indicates that the C=O plane bisects the H-C(6)-H angle)
Half-chair conformation supported by planar nitrogen of lactam moiety (due to N to C=O conjugation)
Greater $A^{1,2}$-strain in **5A** than **5B**
Greater 1,3-diaxial interactions in **5B** than **5A**
$A^{1,2}$-strain must be more destabilizing than 1,3-diaxial interactions

Figure 2-8. Establishment of relative configuration of **5.**



Scheme 2-2. Annulation of 1,3-azadienes with thiodiglycolic anhydride **3c.**

When *tert*-butyl-bearing imines are employed, base-mediated methylation of the acid leads to incessant ring-opening and instead affords highly functionalized x,b-unsaturated acrylates such as **6b2'** and **6c2'**. Although this came as a surprise to us since no ring-opening occurred when the styrenyl motif was replaced by a phenyl group, we now believe that the extended conjugation provides a driving force for the ring opening. Nevertheless, these highly functionalized internally substituted dienes represent important intermediates in their own right, thus, prompting us to explore the transformation further. In the event, we have found that even some aryl-bearing azadienes can afford the versatile dienes (see **6d2'**-**6f2'**). Encouragingly, ring-opening can be mitigated by performing the methylation under acidic conditions (see **6b2**, **6c2**, and **6j2**).

2.3.3: Synthesis of piperidinonates from glutaric anhydrides

The [4 + 2] cycloaddition strategy described so far is not limited to cyclic anhydrides bearing an endocyclic heteroatom such as diglycolic anhydride **3b** and thiodiglycolic anhydride **3c**. In work that was mostly done by two undergraduate students in our lab (Hannah Braunstein and Monique Khim), but included here for purposes of completeness, we have found that inert anhydrides **3a** and **3d** react satisfactorily with α,β-unsaturated imines, at elevated temperatures, to afford the corresponding piperidinonates depicted in Scheme 3 (Scheme 2-3, see **7a**−**r**). The amenability of **3e** to this hexannulation protocol has set the stage for the installation of α-amido quaternary centers. Contrary to **3e**, anhydride **3f** fails to furnish the desired cycloadducts, even at 150 ^{o}C, presumably due to steric congestion.

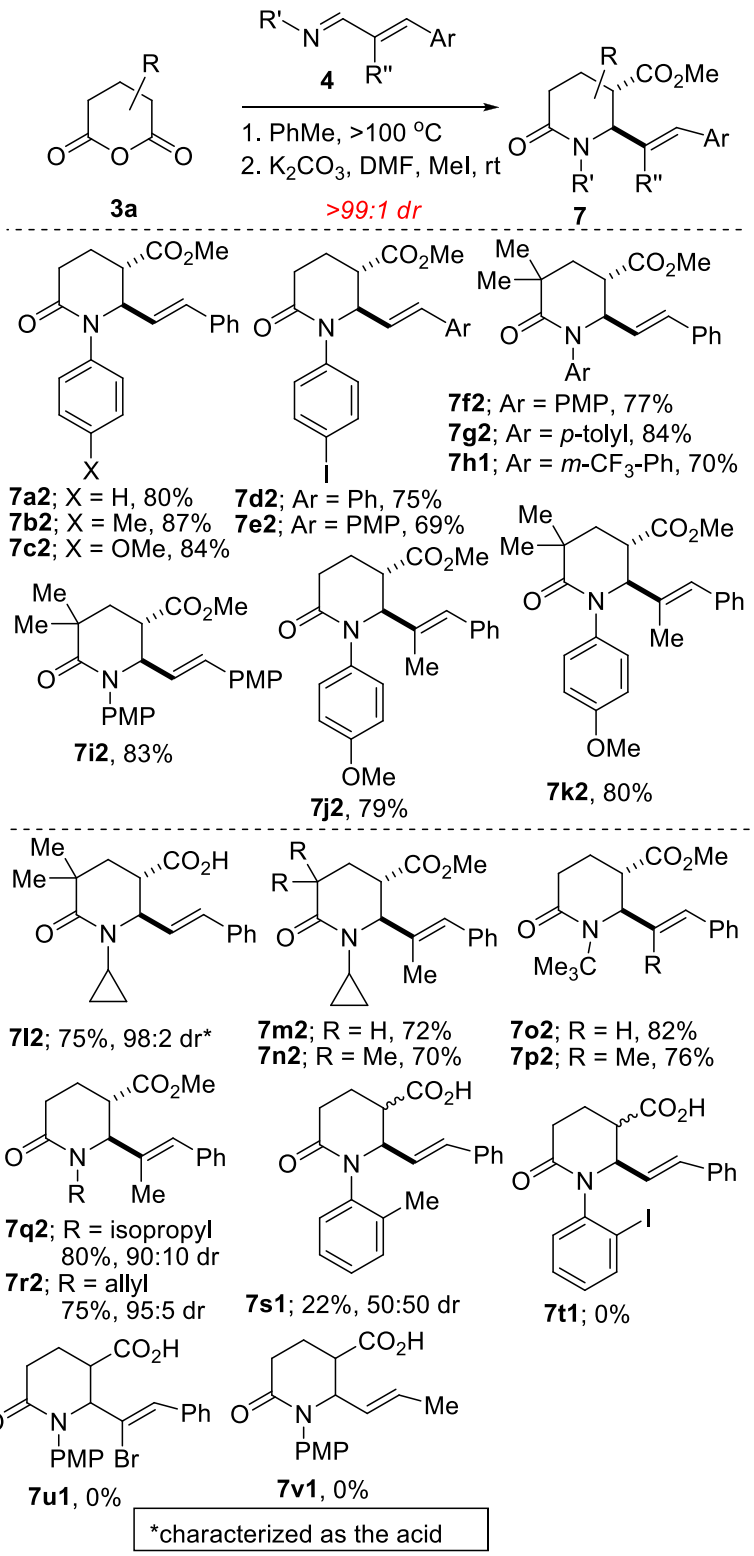
Not all α,β-unsaturated imines that we have evaluated react efficiently and stereoselectively with the cyclic anhydrides employed in these studies. For instance, *ortho*-

substituted *N*-aryl-azadienes such as **4w/x** barely react with **3a/b**. Furthermore, internally substituted but sterically encumbered alkenyl imines do not react with glutaric anhydride (see **7u1**). Additionally, the importance of having the styrenyl motif is highlighted by observations that azadienes derived from *trans*-crotonaldehyde fail to furnish the desired allylic lactams (see **7v1**). In these cases, hydrolysis of the azadiene and concomitant nucleophilic attack of the anhydride by the ensuing amine are observed. Performing the reaction in the presence of molecular sieves fails to negate the hydrolysis.

2.3.4: Synthesis of allylic piperazinonates

The 2-oxopiperazine motif (see highlighted rings in Fig. 2-9) constitutes the core of several alkaloid natural products and pharmaceuticals. It is a privileged substructure whose deoxygenated variant (*i.e.,* the piperazine motif) ranks among the top two *N*-heterocycles in the U.S. FDA-approved-pharmaceuticals.[157] 2-Piperazinones continue to play essential roles as conformationally-constrained peptidomimetics given that they mimic inverse γ-turns in peptides, which in turn play critical roles in the secondary structures of proteins.[174]

Within this research-suitable platform, is a subset of molecules (examples of which are depicted in Fig. 2-9) that possesses vicinal stereocenters. However, regio- and stereoselective methods to achieve *vicinal difunctionalization* are relatively rare, in part because sequential substitution of a 2- or 3-substituted piperazine derivative is either *not tolerated* or *only marginally tolerated* in most of the existing C-2 and C-3 functionalization strategies.[175] Indeed, modular and reliable approaches to carbo-monosubstituted piperazines are still at a premium as evident by the fact that over 80% of small-molecule piperazine pharmaceuticals contain substitution only at the two nitrogen atoms.[175]



Scheme 2-3. Annulation of 1,3-azadienes with glutaric anhydride derivatives

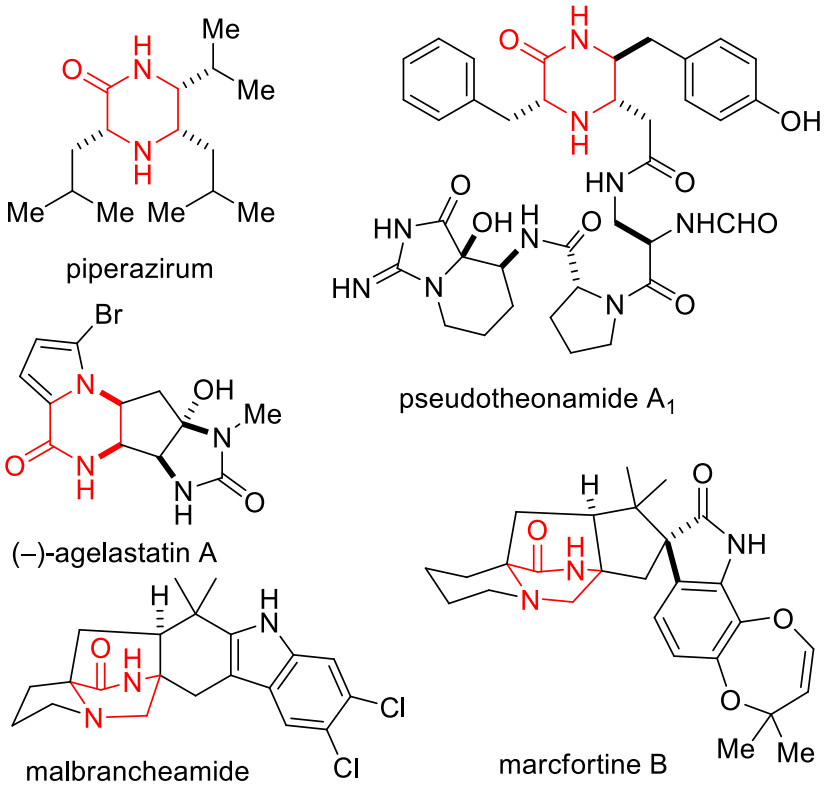


Fig 2-9 Examples of biologically active 2-oxopiperazines

Nevertheless, the architectural complexity and biological significance of vicinally functionalized 2-oxopiperazine derivatives continue to inspire the synthesis community toward developing increasingly more efficient strategies for their construction, peripheral functionalization and evaluation of structure-activity relationships (*i.e.*, SAR). Examples of some well-heeled strategies for accessing carbo-functionalized piperazines and ketopiperazines include those employed by Stoltz[176] (using Pd-catalyzed asymmetric allylic alkylation), Kokotos[177] (using organocatalysis), Bode[39, 178] (using SnAP reagents), Aggarwal[179, 180] (using α-phenylvinylsulfonium salts), Tiecco[181] (using vinyl selenones), MacMillan[68, 69] (using photoredox catalysis), Schafer[182, 183] (using catalytic alkylamination/reduction), Xia[184] (using

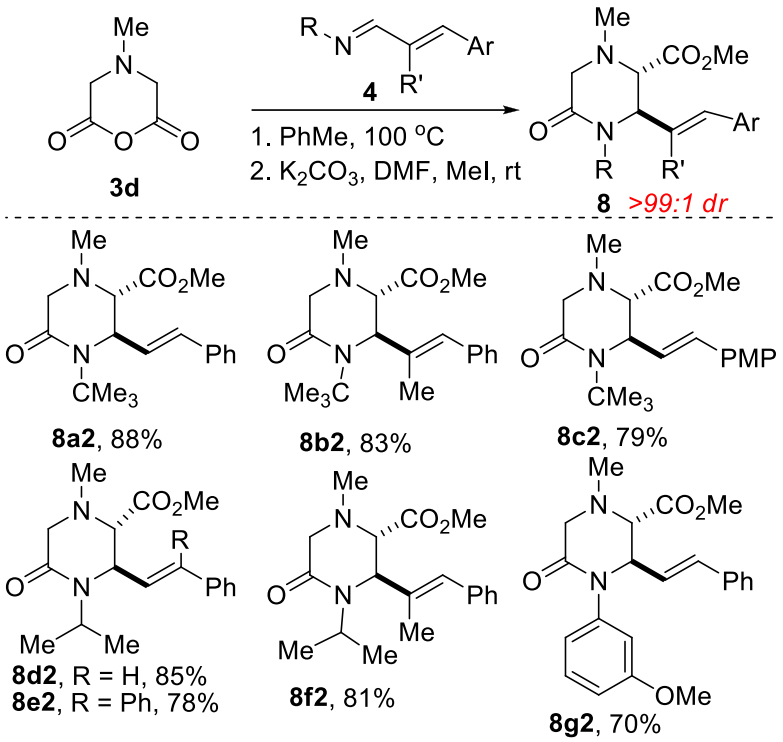
aziridines), Carreira[185, 186] (using spirocyclic 3-oxetanones), Wolfe[187] (using Pd-catalyzed intramolecular carboamination), Mendoza[188] (using aluminum organometallics) and Krasavin[168, 189] (using aryl aldimines such and *N*-tosyl anhydrides).

Being cognizant of the biological relevance of functionalized ketopiperazines, and in the wake of our recent findings on the morpholine, thiomorpholine, and piperidine heterocycles, we next sought to explore the reactivity of *N*-heterocyclic anhydrides such as **3d1/2** with 1,3-azadienes, in view of assembling allylic ketopiperazines of type **8**. Our choice of 1,3-azadienes was mostly guided by observations that common piperazine pharmacophores include *N*-alkylpiperazines (*e.g.*, imatinib, a kinase-inhibiting anticancer agent[190]), *N*-benzylpiperazines (*e.g.*, indinavir, an HIV protease inhibitor[191]) and *N*-arylpiperazines (*e.g.*, piribedil, an antiparkinsonian agent[192]).

As with the other heteroatom-bearing anhydrides, these studies have revealed that piperazinonates such as **8a2-8g2** are affordable when commercially available anhydride **3d** and azadienes of type **4** are refluxed in toluene at 100 ºC. (Scheme 2-4). Internally substituted styrenes are obtainable is good yield (see **8b2**, **8e2**, and **8f2**).

2.4: Conclusion

Modular, cost-efficient, and diastereoselective expansion of the CCR with 1,3-azadienes and a library of cyclic anhydride derivatives has been successful in forming a versatile allylic lactamoyl ester intermediate. *N*-aryl and *N*-alkyl substituted 1,3-azadienes are well tolerated. Internal substitution on the styrene moiety is marginally tolerated. The CCR works well when diglycolic-, glutaric- and *N*-heterocyclic- anhydrides are employed. However, as was homophthalic anhydride in the past, highly acidic thiodiglycolic anhydride is quite problematic.



Scheme 2-4. Annulation of 1,3-azadienes with *N*-heterocyclic anhydride **3d**

S2: Supporting Information for Chapter 2

S2-1: General Experimental Information and Procedures

All experiments involving air and moisture sensitive reagents, such as palladium precatalysts and organolithium reagents, were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 µm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ stain. Unless otherwise indicated, ^1H, ^{13}C, and DEPT-135 NMR, COSY 45, HMQC, and NOESY spectra were acquired using DMSO-d_6, CD_3OD or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^+ data were obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).

General Procedure A: Synthesis of 1,3-azadienes

To a round-bottom flask equipped with a stir bar was added the enal (10 mmol), amine (1 to 1.5 equiv), benzene (50 mL), and anhydrous $MgSO_4$ (2 g). The cloudy suspension was allowed to stir at room temperature. After complete consumption of the amine (based on TLC monitoring), the mixture was filtered through and concentrated under reduced pressure to obtain the crude enamine, which was used in the next step without further purification.
Note: The azadienes need to be stored in the refrigerator when not used immediately.

General Procedure B: Reaction of 1,3-azadienes with hexacyclic anhydrides[1]

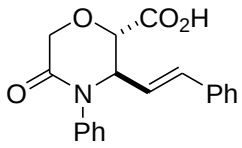
A 5 mL screw-cap vial was flame-dried, evacuated and flushed with nitrogen. A solution of the 1,3-azadiene (1.0 mL, 0.10 M in freshly distilled toluene) was added to the vial at room temperature followed by the cyclic anhydride (1 to 1.1 equiv). The contents were placed in a pre-heated oil bath thermostatted at the desired temperature (e.g., 90 ^oC for diglycolic anhydride). After complete consumption of the enal (as judged by TLC and NMR), the mixture/suspension

was cooled to room temperature and washed several times with petroleum ether, then concentrated under reduced pressure to afford the crude cycloadducts.

General Procedure C: Methyl esterification of cycloadducts

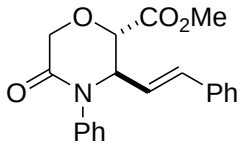
To a stirring suspension of the acid (1 mmol), dissolved in DMF (5 mL), and K_2CO_3 (6 equiv) was added methyl iodide (3 equiv) under nitrogen atmosphere. The reaction mixture was stirred for 12 to 18 h (TLC monitoring). After complete conversion, it was diluted with water and extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired ester.

S2-2: Hexannelation of 1,3-azadienes with diglycolic anhydride



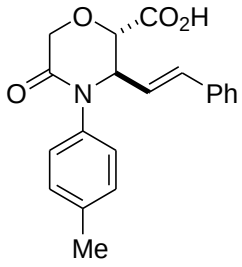
5a1

Prepared from imine **4a** (207 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv), using General Procedure B. T = 90 ºC, time = 18 h. An analytical sample was obtained after a series of washes with petroleum ether. 1H NMR (400 MHz, CDCl3) δ 12.86 (1H, s), 7.56 to 7.12 (5H, m), 6.49 to 6.34 (2H, m), 4.90 (1H, d), 4.58 (2H, dd), 4.20 (1H, d). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 167.6, 140.0, 138.3, 137.4, 136.0, 136.0, 134.8, 134.3, 132.7, 131.9, 130.5, 129.8, 129.8, 129.6, 129.6, 129.4, 129.2, 129.1, 129.0, 128.8, 128.8, 128.4, 127.6, 127.3, 127.2, 125.8, 125.3, 125.1, 121.0, 75.7, 72.1, 69.8, 68.4, 65.3, 64.9, 63.8. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{17}NO_4$ 323.1158; found 323.1163.



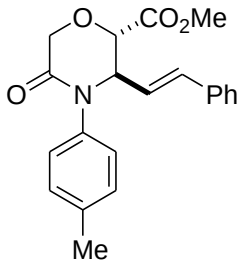
5a2

Prepared from crude **5a1** using General Procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 280 mg, 83% over 2 steps, >99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 to 7.19 (10H, m), 6.48 (1H, d), 6.35 (1H, dd), 4.85 (1H, d), 4.75 (1H, dd), 4.53 (1H, d), 4.27 (1H, d), 3.77 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.66, 165.73, 139.87, 135.55, 134.57, 129.49, 129.45, 129.26, 129.08, 128.78, 128.56, 128.35, 127.83, 127.01, 126.78, 124.74, 119.84, 75.79, 65.51, 63.26, 52.07. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{20}H_{19}NO_4$ 337.1314; found 337.1317.



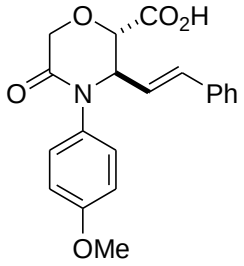
5b1

Prepared from imine **4c** (221 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv), using General Procedure B. T = 90 °C, time = 18 h. An analytical sample was obtained after a series of washes with cold petroleum ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (1H, s, broad), 7.40 to 7.11 (9H, m), 6.47 to 6.32 (2H, m), 4.85 (2H, m), 4.57 (2H, m), 2.30 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 167.7, 137.7, 137.3, 135.6, 134.5, 130.5, 129.1, 128.9, 127.2, 127.2, 124.8, 75.5, 65.4, 63.8, 21.5. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{20}H_{19}NO_4$ 337.1314; found 337.1318.



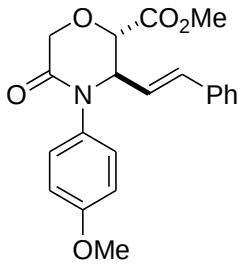
5b2

Prepared from crude **5b1** using General Procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 313 mg, 89% over 2 steps, >99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 to 7.11 (9H, m), 6.45 (1H, d), 6.32 (1H, dd), 4.82 to 4.47 (4H, dd), 3.88 (3H, s), 2.38 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 165.8, 137.7, 137.2, 135.6, 134.4, 130.1, 128.8, 128.5, 126.8, 126.8, 124.8, 75.8, 65.5, 63.3, 53.0, 21.2. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{21}NO_4$ 351.1417; found 351.1421.



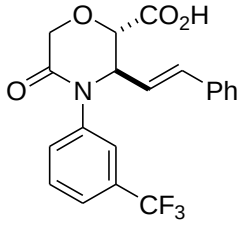
5c1

Prepared from imine **4b** (237 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv), using General Procedure B. T = 90 °C, time = 18 h. An analytical sample was obtained after a series of washes with cold petroleum ether. Yield = 300 mg, 84%. ^{1}H NMR (400 MHz, MeOH) δ 7.39 to 7.12 (5H, m), 6.92 (2H, d), 6.48 (2H, d), 4.79 (1H, d), 4.65 to 4.61 (2H, dd), 4.44 (1H, d), 3.77 (3H, s). ^{13}C NMR (101 MHz, MeOH) δ 170.9, 167.4, 159.1, 135.9, 134.4, 134.1, 132.5, 128.3, 128.1, 128.1, 127.9, 127.9, 126.4, 124.8, 114.1, 75.4, 64.6, 63.8, 54.5. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{20}H_{19}NO_5$ 353.1263; found 353.1267.



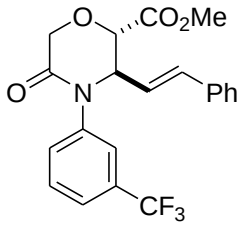
5c2

Prepared from crude **5c1** using General Procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 338 mg, 92% over 2 steps, >99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 to 7.25 (5H, m), 7.13 (2H, d), 6.88 (2H, d), 6.42 to 6.28 (2H, m), 4.77 to 4.44 (3H, m), 3.87 to 3.75 (7H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 165.9, 158.8, 136.3, 135.5, 134.6, 132.5, 129.3, 128.8, 128.7, 128.7, 128.5, 128.3, 126.8, 126.7, 124.7, 114.1, 75.7, 65.5, 63.5, 55.5, 52.7. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{21}NO_5$ 367.1420; found 367.1416.



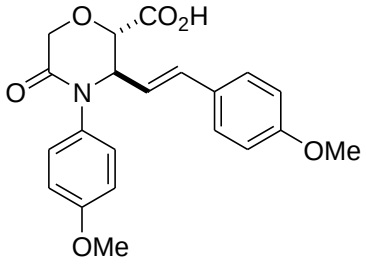
5d1

Prepared from imine **4e** (275 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv), using General Procedure B. T = 100 °C, time = 18 h. An analytical sample was obtained after a series of washes with cold petroleum ether^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (1H, s), 7.69 to 7.24 (4H, m), 6.43 to 6.30 (2H, m), 4.86 to 4.74 (2H, dd), 4.60 to 4.48 (2H, dd). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.97, 163.48, 139.95, 139.84, 137.52, 137.33, 135.28, 133.90, 132.28, 132.10, 131.95, 131.67, 131.62, 131.30, 131.11, 130.81, 130.18, 130.10, 129.69, 129.46, 129.28, 129.23, 129.13, 129.09, 128.82, 128.77, 128.56, 128.32, 128.23, 127.66, 126.94, 126.84, 126.15, 125.72, 124.97, 124.94, 124.19, 124.15, 124.11, 123.94, 123.42, 122.24, 75.73, 65.02, 63.83. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{20}H_{16}F_3NO_4$ 391.1031; found 391.1022.



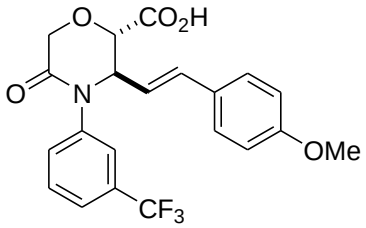
5d2

Prepared from crude **5d1** using General Procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 304 mg, 75% over 2 steps, >99:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 to 7.25 (4H, m), 6.44 (1H, d), 6.28 (1H, dd), 4.85 (1H, d), 4.72 (1H, d), 4.56 (1H, d), 4.30 (1H, d), 3.77 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.15, 165.81, 140.32, 136.82, 132.02, 131.69, 131.35, 130.64, 130.06, 129.98, 129.58, 129.35, 129.17, 128.80, 128.75, 128.72, 128.63, 128.56, 127.99, 126.83, 126.77, 124.94, 124.62, 124.59, 124.55, 124.51, 124.18, 123.91, 123.87, 123.83, 123.79, 122.85, 122.23, 75.76, 65.52, 63.93, 53.03. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{18}F_3NO_4$ 405.1188; found 405.1194.



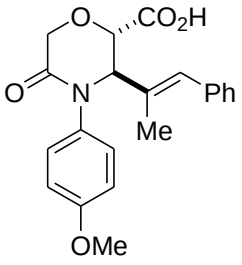
5e1

Prepared from imine **4f** (267 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv), using General Procedure B. T = 90 ºC, time = 18 h. Yield = 314 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (1H, s, br), 7.51 to 6.77 (8H, m), 6.37 to 6.13 (2H, m), 4.81 to 4.20 (4H, m), 3.76 to 3.67 (6H, overlapping singlets). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 167.5, 159.8, 158.9, 136.2, 134.1, 132.2, 130.0, 129.3, 129.1, 128.7, 128.4, 128.3, 128.3, 128.1, 125.4, 122.2, 122.1, 114.2, 114.1, 75.9, 68.1, 64.4, 63.8, 55.4, 55.3. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{21}NO_6$ 383.1369; found 383.1376.



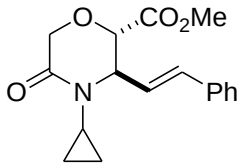
5f1

Prepared from imine **4h** (305 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedure B. T = 100 ºC, time = 22 h. Yield = 295 mg, 70%. ^{1}H NMR (400 MHz, MeOH) δ 7.61 to 7.49 (4H, m) 7.32 (2H, d), 6.83 (2H, d), 6.44 to 6.29 (2H, m), 4.87 to 4.23 (4H, m), 3.76 (3H, s). ^{13}C NMR (101 MHz, MeOH) δ 170.8, 167.3, 160.0, 140.6, 134.1, 132.5, 131.0, 130.8, 129.9, 129.6, 129.4, 128.4, 127.7, 124.2, 124.1, 124.0, 123.2, 122.1, 113.7, 75.6, 64.8, 63.8, 54.3. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{21}H_{18}F_3NO_5$ 421.1137; found 421.1143.



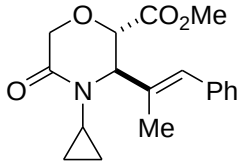
5g1

Prepared from imine **4i** (251 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedure B. T = 90 ºC, time = 22 h. Yield = 290 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.10 (1H, s, br), 7.36 to 6.83 (9H, m), 6.49 (1H, s), 4.77 to 4.12 (4H, dd), 3.72 (3H, s), 1.86 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 166.3, 159.5, 136.9, 133.8, 131.4, 130.2, 129.3, 129.2, 128.2, 127.9, 126.1, 114.5, 74.3, 65.3, 55.8, 15.7. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{21}H_{21}NO_6$ 383.1369; found 383.1376.



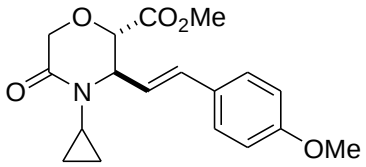
5h2

Prepared from imine **4k** (171 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedures B and C. T = 90 ºC, time = 12 h. Yield = 217 mg, 72%, 80:20 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 to 7.25 (10H, m), 6.69 to 6.56 (2H, dd), 6.26 to 6.14 (2H, dd), 4.51 to 4.00 (8H, dd), 3.80 to 3.71 (6H, m), 2.65 to 2.60 (2H, m), 0.99 to 0.48 (8H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.5, 167.8, 167.3, 135.6, 135.6, 133.9, 128.7, 128.7, 128.5, 128.4, 126.8, 126.7, 125.1, 122.5, 76.3, 75.5, 68.7, 68.1, 60.9, 60.2, 52.7, 52.0, 28.6, 28.3, 8.5, 7.4, 6.3, 5.0. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{17}H_{19}NO_4$ 301.1314; found 301.1310.



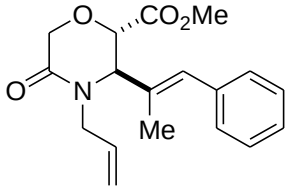
5i2

Prepared from imine **4l** (185 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedures B and C. T = 90 ºC, time = 12 h. Yield = 221 mg, 70%, 87:13 dr. ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 to 7.14 (5H, m), 6.65 (1H, s), 4.60 to 4.15 (4H, m), 3.79 (3H, s), 2.65 to 2.49 (1H, m), 1.89 (3H, s), 1.07 to 0.54 (4H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.3, 136.6, 133.4, 131.6, 130.1, 129.3, 129.0, 128.4, 127.3, 127.2, 126.8, 119.6, 76.8, 74.8, 68.2, 67.6, 65.7, 65.6, 65.1, 52.8, 52.6, 28.6, 28.4, 15.2, 14.4, 8.5, 8.3, 5.7, 5.0. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{18}H_{21}NO_4$ 315.1471; found 315.1476.



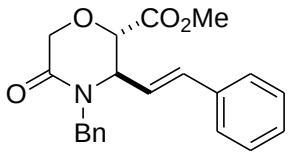
5j2

Prepared from imine **4t** (201 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedures B and C. T = 90 °C, time = 16 h. Yield = 268 mg, 81%, 85:15 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 to 7.22 (4H, major & minor), 6.89 to 6.72 (4H, mixture), 6.56 to 6.47 (2H, mixture), 6.18 to 5.96 (2H, mixture), 4.47 to 4.09 (8H, mixture), 3.80 to 3.71 (6H, mixture), 2.60 to 2.47 (2H, mixture), 0.99 to 0.48 (8H, mixture). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.43, 169.61, 167.83, 167.38, 159.89, 159.83, 135.05, 133.33, 130.39, 129.71, 128.92, 128.85, 128.31, 128.09, 127.99, 126.78, 126.47, 122.70, 120.09, 114.5, 114.4, 76.3, 75.6, 68.67, 68.05, 65.35, 61.02, 55.34, 55.29, 52.64, 52.62, 29.70, 28.55, 8.56, 7.37, 6.33, 5.34. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{18}H_{21}NO_5$ 331.1420; found 331.1425.



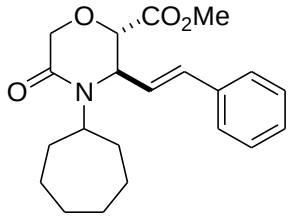
5k2

Prepared from imine **4v** (185 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedures B and C. T = 90 °C, time = 16 h. Yield = 277 mg, 88%, 92:8 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 to 6.97 (5H,m), 6.48 (1H, s), 5.81 to 5.67 (1H, m), 5.30 to 5.12 (2H, m), 4.79, to 4.21 (5H, m), 3.79 (3H, s), 3.30 to 3.22 (1H, dd), 1.84 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 169.7, 168.7, 166.4, 137.5, 136.4, 133.9, 132.9, 132.5, 132.3, 132.0, 131.8, 130.2, 129.8, 129.1, 129.0, 128.4, 128.2, 128.2, 128.2, 127.4, 127.3, 126.8, 126.6, 119.2, 118.9, 118.4, 116.6, 77.5, 77.4, 77.2, 76.8, 74.8, 71.3, 69.4, 68.6, 68.1, 67.8, 67.4, 65.3, 63.6, 52.7, 52.2, 52.0, 50.5, 46.4, 46.3, 41.3, 40.7, 17.2, 14.7, 14.2. **HRMS-EI+** (*m/z*): calc'd for $C_{18}H_{21}NO_4$ 315.1471; found 315.1475.



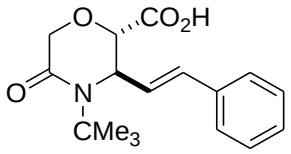
5l2

Prepared from imine **4u** (221 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedures B and C. T = 90 ºC, time = 16 h. Yield = 277 mg, 79%, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 to 6.76 (10 H, m), 6.74 to 6.70 (1H, dd), 6.59 to 6.51 (1H, dd), 5.56 (1H, d), 4.84 (1H, d), 4.42 to 4.35 (2H, m), 3.77 to 3.66 (2H, m), 3.49 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.47, 166.39, 137.01, 136.39, 135.76, 134.93, 131.68, 129.51, 129.37, 129.35, 129.17, 129.03, 128.98, 128.90, 128.75, 128.21, 127.22, 127.14, 124.77, 75.45, 65.44, 58.58, 52.62, 47.07. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{21}H_{21}NO_4$ 351.1471; found 351.1476.



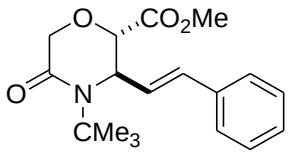
5m2

Prepared from imine **4m** (227 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedures B and C. T = 90 ºC, time = 16 h. Yield =282 mg, 79%, 81:19 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 to 7.21 (5H, m), 6.73 to 6.51 (1H, dd), 6.33 to 6.14 (1H, dd), 4.64 to 3.60 (8H, m), 1.93 to 1.36 (12H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.77, 170.00, 167.60, 165.07, 164.74, 152.88, 135.73, 134.77, 132.95, 131.34, 129.16, 128.80, 128.75, 128.71, 128.55, 128.49, 128.41, 128.02, 127.81, 127.29, 126.78, 126.70, 125.10, 124.86, 108.25, 81.25, 77.55, 77.23, 77.11, 76.91, 76.29, 71.47, 68.71, 68.11, 68.05, 67.80, 65.14, 59.05, 58.40, 57.24, 56.87, 54.08, 52.69, 52.65, 52.03, 49.94, 44.95, 35.04, 33.41, 33.28, 32.73, 32.63, 32.57, 31.89, 28.06, 27.71, 27.46, 27.29, 27.27, 26.13, 25.48, 25.34, 25.11, 25.02, 24.07. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{21}H_{27}NO_4$ 357.1940; found 357.1944.



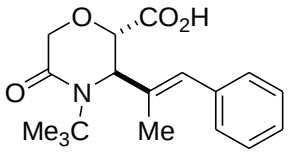
5n1

Prepared from imine **4n** (187 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedure B. T = 90 °C, time = 12 h. An analytical sample was obtained after a series of washes with cold petroleum ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 to 7.22 (5H, m), 6.63 (1H, d), 6.30 (1H, dd), 4.95 (1H, d), 4.71 to 4.53 (2H, dd) , 4.21 (1H, d), 1.40 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 167.8, 135.6, 133.0, 128.8, 128.8, 128.5, 127.4, 126.8, 126.7, 76.3, 65.6, 61.2, 59.1, 28.4. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{17}H_{21}NO_4$ 303.1471; found 303.1467.



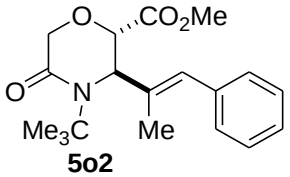
5n2

Prepared from crude **5n1** using General Procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 260 mg, 82% over 2 steps, 96:4 dr. ^{1}H NMR (400 MHz, CDCl3) δ 7.55 to 7.16 (5H, m), 6.66, (1H, d), 6.26 to 6.09 (1H, dd), 4.83 (1H, d), 4.58 to 4.32 (2H, dd), 4.25 (1H, d), 3.74 (3H, s), 1.43 (9H, s). ^{13}C NMR (101 MHz, CDCl3) δ 170.4, 167.8, 135.7, 135.7, 134.5, 134.0, 132.7, 131.3, 129.1, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 127.7, 127.2, 127.1, 126.7, 126.6, 125.7, 80.2, 78.4, 77.6, 77.6, 77.3, 77.0, 76.6, 71.8, 71.7, 70.4, 68.6, 68.1, 68.0, 65.7, 59.2, 58.4, 57.3, 56.6, 52.6, 52.0, 51.8, 51.0, 45.8, 45.3, 36.5, 29.9, 28.8, 28.4, 28.1, 27.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{18}H_{23}NO_4$ 317.1627; found 317.1629.



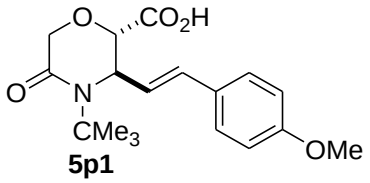
5o1

Prepared from imine **4o** (201 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedure B. T = 90 °C, time = 18 h. An analytical sample was obtained after a series of washes with cold petroleum ether. ^{1}H NMR (400 MHz, DMSO) δ 13.45 (1H, s, br), 7.37 to 7.22 (5H, m), 6.37 (1H, s), 4.67 to 4.54 (2H, dd), 4.28 to 4.09 (2H, dd), 1.91 (3H, s), 1.37 (9H, s). ^{13}C NMR (101 MHz, DMSO) δ 172.2, 166.8, 137.2, 136.9, 129.2, 128.8, 127.3, 127.0, 74.0, 65.4, 61.4, 58.2, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 27.9, 16.2. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{18}H_{23}NO_4$ 317.1627; found 317.1627.



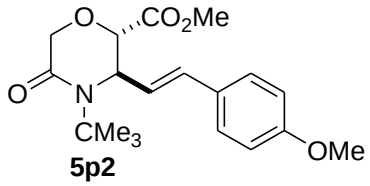
5o2

Prepared from crude **5o1** using General Procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 252 mg, 76% over 2 steps, >99:1 dr. 1H NMR (400 MHz, CDCl3) δ 7.36 to 7.20 (5H, m), 6.48 (1H, s), 4.62 to 4.53 (3H, m), 4.23 (1H, d), 3.73 (3H, s), 1.97 (3H, s), 1.46 (9H, s). ^{13}C NMR (101 MHz, CDCl3) δ 170.9, 167.0, 136.8, 135.3, 129.0, 128.3, 127.1, 77.5, 77.1, 76.8, 74.8, 65.8, 61.6, 60.4, 58.8, 52.8, 28.2, 28.0, 16.0, 14.3. 28.2. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{19}H_{25}NO_4$ 331.1784; found 331.1788.



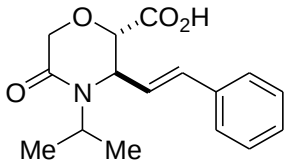
5p1

Prepared from imine **4r** (217 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedure B. T = 90 ºC, time = 18 h. An analytical sample was obtained after a series of washes with cold petroleum ether. 1H NMR (400 MHz, DMSO) δ 13.38 (1H, s, br), 7.41 (2H, d), 6.90 (2H, d), 6.50 (1H, d), 6.30 (1H, dd), 4.74 (1H, d), 4.55 (1H, d), 4.29 to 4.09 (2H, dd), 3.80 (3H, s), 1.36 (9H, s). 13C NMR (101 MHz, DMSO) δ 172.0, 166.7, 159.6, 133.0, 131.2, 129.1, 128.3, 127.2, 114.6, 76.2, 68.8, 65.4, 58.5, 57.7, 56.7, 55.7, 40.7, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 30.0, 29.0, 28.4, 28.2. **HRMS-EI+** (*m/z*): calc'd for $C_{18}H_{23}NO_5$ 333.1576; found 333.1580.



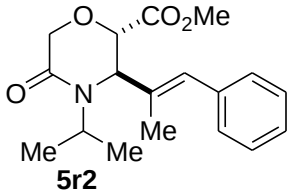
5p2

Prepared from crude **5p1** using General Procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 274 mg, 79% over 2 steps, 93:7 dr. 1H NMR (400 MHz, CDCl3) δ 7.48 (2H, d), 6.88 (2H, d), 6.52 (1H, d), 6.09 (1H, dd), 4.78 (1H, d), 4.55 to 4.34 (2H, dd), 4.19 to 4.15 (1H, dd), 3.79 to 3.71 (6H, overlapping singlets),1.33 (9H, s). 13C NMR (101 MHz, CDCl3) δ 170.5, 166.7, 62.5, 159.8, 152.3, 133.9, 132.1, 130.4, 129.9, 128.4, 128.0, 127.9, 125.4, 123.3, 114.6, 114.2, 114.1, 113.5, 78.6, 77.0, 76.7, 71.8, 68.6, 68.1, 68.0, 65.7, 59.2, 58.3, 57.4, 56.6, 55.3, 52.6, 51.8, 28.8, 28.4. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{25}NO_5$ 347.1733; found 347.1729.



5q1

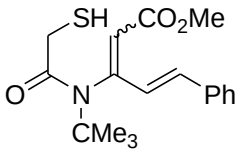
Prepared from imine **4p** (305 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedure B. T = 90 ºC, time = 16 h. Yield = 295 mg, 82%, 83:17 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (1H, s, br), 7.40 to 7.11 (5H, m), 6.62 (1H, d),6.27 to 6.20 (1H, dd), 4.67 to 4.46 (3H, m), 4.39 to 4.21 (1H, m),4.10 (1H, d), 1.27 to 1.18 (6H, dd). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 172.2, 170.7, 167.4, 167.0, 135.6, 135.6, 133.3, 129.2, 128.8, 128.7, 128.5, 128.1, 127.2, 126.9, 126.7, 123.8, 77.6, 77.3, 77.0, 76.4, 75.6, 70.8, 68.8, 68.2, 68.1, 68.1, 67.3, 64.5, 57.0, 55.5, 52.2, 49.0, 47.3, 45.3, 22.4, 20.6, 20.2, 19.6, 19.5. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{16}H_{19}NO_4$ 289.1314; found 289.1318.



5r2

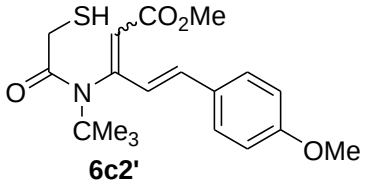
Prepared from imine **4q** (187 mg, 1.0 mmol) and diglycolic anhydride (128 mg, 1.1 equiv) using General Procedures B and C. T = 90 ºC, time = 12 h. Yield =289 mg, 91%, 92:8 dr. 1H NMR (400 MHz, $CDCl_3$) δ 7.36 to 7.20 (5H, m), 6.48 (1H, s), 4.62 to 4.53 (3H, m), 4.23 (1H, d), 3.73 (3H, s), 1.97 (3H, s), 1.46 (6H, dd). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 166.1, 136.7, 135.6, 131.2, 129.7, 128.9, 128.7, 128.5, 128.3, 127.3, 127.2, 127.1, 77.7, 77.6, 77.3, 77.0, 76.7, 74.8, 68.0, 67.3, 64.9, 64.6, 61.8, 60.1, 52.6, 52.4, 51.9, 51.9, 48.0, 46.4, 46.0, 20.2, 30.0, 19.6, 19.3, 19.0, 18.9, 15.5, 14.6. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{18}H_{23}NO_4$ 317.1627; found 317.1622.

S2-3: Hexannelation of 1,3-azadienes with thiodiglycolic anhydride



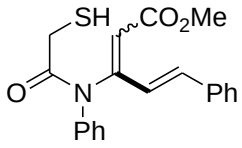
6b2'

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 °C, time = 22 h. Yield = 216.5 mg, 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 11.0 Hz, 1H), 7.53 – 7.39 (m, 2H), 7.33 (q, *J* = 8.5, 7.8 Hz, 3H), 7.24 – 7.17 (m, 1H), 7.02 (d, *J* = 15.6 Hz, 1H), 6.66 (s, 1H), 3.70 (s, 3H), 3.37 (s, 2H), 1.30 (d, *J* = 26.4 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 166.1, 148.0, 143.3, 135.8, 129.8, 129.5, 129.0, 128.8, 127.9, 127.7, 127.5, 124.5, 52.8, 52.6, 51.4, 39.2, 28.6, 28.5, 28.4. **HRMS-EI+** (*m/z*): calc'd for $C_{18}H_{23}NO_3S$ 333.1399; found 333.2458.



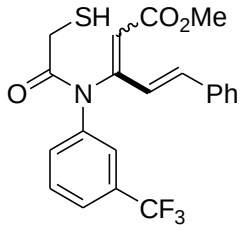
6c2'

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 °C, time = 22 h. Yield = 225.4 mg, 62%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 11.1 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.32 (dd, *J* = 15.5, 11.0 Hz, 1H), 6.97 (d, *J* = 15.4 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.72 (s, 1H), 3.80 (s, 6H), 3.72 (d, *J* = 16.0 Hz, 2H), 3.36 (s, 2H), 3.19 (s, 1H), 1.30 (d, *J* = 26.3 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 166.3, 161.1, 148.8, 143.4, 129.4, 129.0, 128.7, 122.4, 114.4, 55.4, 52.8, 51.5, 51.4, 39.4, 28.6, 28.5. **HRMS-EI+** (*m/z*): calc'd for $C_{19}H_{25}NO_4S$ 363.1504; found 363.4711.



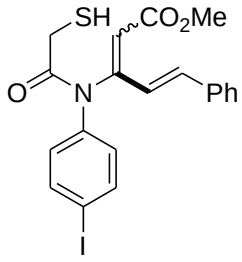
6d2'

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 ºC, time = 22 h. Yield = 278.9 mg, 79%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.40 (s, 1H), 7.82 (d, *J* = 11.1 Hz, 1H), 7.64 – 7.45 (m, 4H), 7.45 – 7.15 (m, 5H), 7.13 – 6.98 (m, 2H), 3.81 (s, 3H), 3.69 (d, *J* = 21.0 Hz, 1H), 3.59 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.8, 149.2, 144.1, 138.1, 137.9, 135.8, 129.9, 129.5, 129.3, 129.0, 127.9, 127.7, 127.6, 124.3, 124.1, 120.1, 120.0, 119.9, 53.1, 40.0. **HRMS-EI+** (*m/z*): calc'd for $C_{20}H_{19}NO_3S$ 353.1086; found 353.47348.



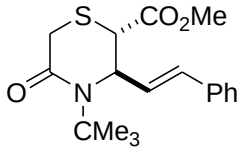
6e2'

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 ºC, time = 22 h. Yield = 345.3 mg, 82%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.80 (s, 1H), 7.96 (s, 1H), 7.82 (dd, *J* = 13.2, 9.4 Hz, 2H), 7.56 – 7.44 (m, 3H), 7.31 (q, *J* = 8.8 Hz, 6H), 7.02 (d, *J* = 15.7 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 167.5, 149.6, 144.4, 130.7, 130.3, 130.0, 129.8, 129.5, 129.0, 128.6, 127.8, 127.6, 124.3, 123.9, 123.4, 122.9, 120.7, 116.4, 116.3, 53.1, 52.7, 40.1. **HRMS-EI+** (*m/z*): calc'd for $C_{21}H_{18}F_3NO_3S$ 421.0959; found 421.4327.



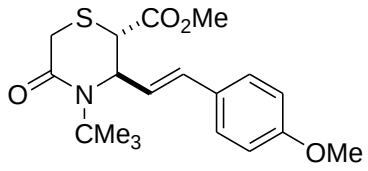
6f2'

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 °C, time = 22 h. Yield = 383.2 mg, 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.51 (s, 1H), 7.92 (s, 1H), 7.62 (dd, 4H), 7.56 – 7.42 (m, 5H), 7.04 (d, 1H), 3.84 (s, 3H), 3.55 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 149.8, 144.2, 137.8, 135.9, 130.2, 129.2, 129.0, 128.9, 127.7, 127.6, 124.1, 123.9, 121.8, 87.8, 53.6, 40.3. **HRMS-EI+** (*m/z*): calc'd for $C_{20}H_{18}INO_3S$ 479.0052; found 479.3313.



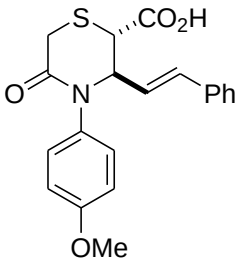
6b2

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 °C, time = 22 h. Yield = 166.7 mg, 50%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (td, *J* = 22.3, 20.1, 11.9 Hz, 5H), 6.52 (d, *J* = 16.1 Hz, 1H), 6.22 (dd, *J* = 16.0, 4.2 Hz, 1H), 5.28 (s, 1H), 3.92 (d, *J* = 2.9 Hz, H), 3.73 (s, 3H), 3.39 (d, *J* = 15.1 Hz, 1H), 3.17 (dd, *J* = 14.8, 10.3 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 166.7, 135.9, 135.8, 132.7, 131.3, 128.7, 128.6, 128.3, 128.2, 128.0, 126.7, 126.6, 59.2, 58.3, 58.2, 53.1, 50.0, 47.3, 47.2, 30.0, 29.9, 28.9, 28.4. **HRMS-EI+** (*m/z*): calc'd for $C_{18}H_{23}NO_3S$ 333.1399; found 333.4451.



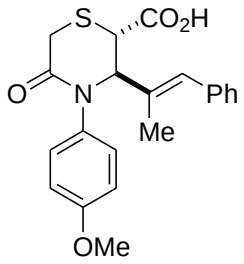
6c2

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 ºC, time = 22 h. Yield = 207.2 mg, 57%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (m, 2H), 6.91 – 6.69 (m, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.07 (dd, *J* = 15.9, 4.4 Hz, 1H), 5.25 (d, *J* = 4.7 Hz, 1H), 3.90 (d, *J* = 2.9 Hz, 1H), 3.84 – 3.53 (m, 6H), 3.39 (t, *J* = 15.7 Hz, 1H), 3.15 (d, *J* = 14.8 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 166.8, 160.0, 131.0, 130.9, 130.7, 128.7, 128.4, 127.6, 114.2, 114.1, 59.2, 58.4, 58.2, 55.4, 55.3, 55.2, 53.0, 47.7, 47.5, 31.2, 28.9, 28.6, 28.4. **HRMS-EI+** (*m/z*): calc'd for $C_{18}H_{23}NO_3S$ 363.1504; found 363.4711.



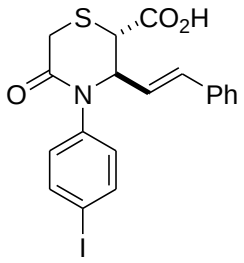
6g1

Prepared from imine **4b** (237 mg, 1.0 mmol) and thiodiglycolic anhydride (132 mg, 1.0 equiv), using General Procedure B. T = 60 ºC, time = 12 h. An analytical sample was obtained after a series of washes with cold petroleum ether. Yield = 258 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (1H, br. S), 7.52 to 7.09 (7H, m), 6.91 to 6.79 (2H, d), 6.58 to 6.32 (2H, m), 4.85 to 4.83 (1H, dd), 3.80 to 3.32 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.19, 168.27, 158.78, 135.84, 134.61, 134.11, 130.75, 129.26, 128.06, 126.88, 122.31, 118.93, 66.58, 55.96, 44.84, 28.34. **HRMS-EI+** (*m/z*): calc'd for $C_{20}H_{19}NO_4S$ 369.1035; found 369.1039.



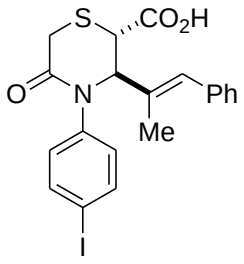
6h1

Prepared from imine **4i** (251 mg, 1.0 mmol) and thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedure B. T = 60 °C, time = 12 h. Yield = 280 mg, 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (1H, s br), 7.55 to 7.08 (5H, m), 6.95 to 6.81 (2H, d), 6.41 (1H, s), 4.89 (1H, d), 3.85 to 3.30 (6H, m), 1.86 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.48, 167.36, 158.59, 136.78, 135.18, 133.62, 130.15, 129.38, 129.02, 128.75, 127.09, 118.12, 71.05, 55.45, 43.98, 28.66, 18.23. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{21}NO_4S$ 383.1191; found 383.1187.



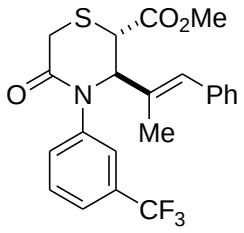
6f1

Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedure B. T = 60 °C, time = 16 h. Yield = 363 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (1H, s br), 7.66 to 7.57 (2H, d), 7.38 to 7.19 (5H, m), 6.95 (2H, d), 6.46 to 6.39 (2H, m), 4.86 to 4.81 (1H, dd), 3.73 to 3.36 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.84, 168.17, 141.39, 138.6, 137.99, 136.24, 134.74, 129.78, 128.78, 126.90, 125.35, 93.71, 66.28, 44.34, 28.27. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{16}INO_3S$ 464.9896; found 465.0007.



6i1

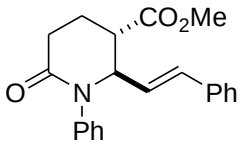
Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedure B. T = 60 ^{o}C, time = 22 h. Yield = 407 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (1H, s br), 7.81 to 7.03 (9H, m), 6.59 (1H, s), 4.88 (1H, d), 3.83 to 3.36 (3H, m), 1.87 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.93, 167.29, 141.96, 139.91, 138.46, 132.90, 130.73, 129.19, 128.45, 128.03, 127.41, 93.28, 70.43, 43.23, 28.53, 18.53. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{20}H_{18}INO_3S$ 479.0052; found 479.0061.



6j2

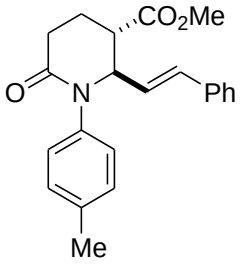
Prepared from thiodiglycolic anhydride (132 mg, 1.0 equiv) using General Procedures B & C. T = 60 ^{o}C, time = 22 h. Yield = 387 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 to 7.18 (9H, m), 6.62 (1H, s), 4.93 (1H, d), 3.93 to 3.87 (4H, m), 3.57 to 3.39 (2H, m), 1.96 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.37, 165.93, 152.71, 142.86, 141.45, 136.25, 133.03, 131.15, 130.83, 129.73, 129.70, 129.54, 128.52, 128.32, 127.40, 124.35, 124.31, 124.06, 122.78, 70.83, 53.38, 43.75, 29.05, 18.18. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{23}H_{20}F_3NO_3S$ 435.1116; found 435.1121.

S2-4: Hexannelation of 1,3-azadienes with glutaric- or 2,2-dimethylglutaric anhydride



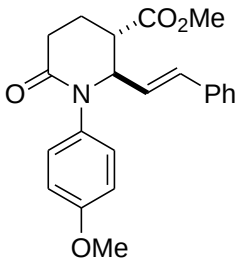
7a2

Prepared from imine **4a** and glutaric anhydride (114 mg, 1 equiv) using General Procedures B and C. Temp = 105 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 268 mg, 80% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 to 7.05 (10H, m), 6.39 (1H, d), 6.15 to 6.09 (1H, dd), 4.92 to 4.89 (1H, d), 3.79 (3H, s), 2.97 to 2.93 (1H, m), 2.73 to 2.61 (2H, m), 2.42 to 2.25 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 169.3, 141.9, 135.8, 134.8, 133.3, 129.1, 128.8, 128.2, 127.7, 127.3, 126.5, 124.4, 63.8, 52.5, 44.5, 29.9, 20.4. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{21}NO_3$ 335.1521; found 335.1525.



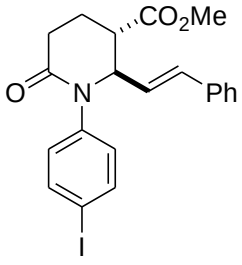
7b2

Prepared from imine **4c** (221 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. T = 105 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 304 mg, 87% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 to 7.00 (9H, m), 6.41 to 6.34 (1H, d), 6.18 to 6.10 (1H, dd), 4.90 to 4.87 (1H, dd), 3.77 (3H, s), 2.96 to 2.93 (1H, m), 2.70 to 2.61 (2H, m), 2.41 to 2.28 (5H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 169.4, 139.3, 137.0, 135.9, 134.8, 133.2, 130.0, 129.8, 129.3, 128.7, 128.3, 128.2, 128.1, 127.7, 127.47, 127.3, 126.7, 126.6, 124.5, 63.9, 52.5, 44.5, 29.9, 21.1, 20.8. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{22}H_{23}NO_3$ 349.1678; found 349.1672.



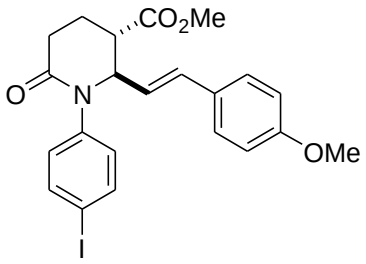
7c2

Prepared from imine **4b** (237 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. T = 105 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100) then 100% MeOH. Yield = 307 mg, 84% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 to 7.15 (7H, m), 6.87 (2H, d), 6.38 to 6.31 (1H, d), 6.13 to 6.09 (1H, dd), 4.69 to 4.67 (1H, dd), 3.77 to 3.72 (6H, ss), 2.89 to 2.72 (1H, t), 2.65 to 2.56 (2H, m), 2.39 to 2.23 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 169.5, 158.4, 135.9, 134.9, 134.7, 133.2, 129.3, 128.8, 128.7, 128.7, 128.3, 128.2, 127.6, 126.7, 126.6, 124.5, 114.4, 64.1, 55.4, 52.4, 44.4, 29.9, 20.2. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{22}H_{23}NO_4$ 365.1627; found 365.1633.



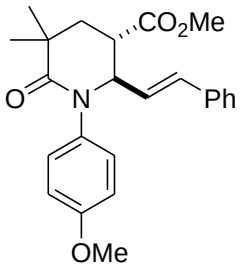
7d2

Prepared from imine **4d** (333 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. T = 105 °C, time = 22 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 346 mg, 75% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d), 7.46 to 7.23 (5H, m), 7.04 (2H, d), 6.37 to 6.33 (1H, d), 6.16 to 6.08 (1H, dd), 4.88 to 4.85 (1H, dd), 3.78 (3H, s), 2.95 to 2.93 (1H, m), 2.69 to 2.61 (2H, m), 2.37 to 2.24 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 169.2, 141.7, 138.5, 138.3, 138.3, 137.7, 135.6, 135.1, 133.5, 131.3, 130.4, 129.7, 129.4, 129.2, 128.8, 128.5, 128.5, 128.4, 127.1, 126.7, 126.6, 124.1, 123.9, 92.5, 63.7, 52.3, 44.7, 29.8, 20.6. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{21}H_{20}INO_3$ 461.0488; found 461.0492.



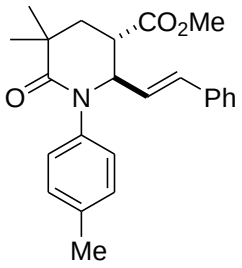
7e2

Prepared from imine **4g** (363 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. T = 105 ºC, time = 22 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 339 mg, 69% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (2H, d), 7.28 to 7.16 (3H, m), 7.04 to 6.98 (2H, m), 6.81 (2H, d), 6.27 (1H, d), 5.95 to 5.91 (1H, dd), 4.82 to 4.79 (1H, dd), 3.78 to 3.74 (6H, s,s), 2.93 to 2.90 (1H, m), 2.61 to 2.57 (2H, m), 2.38 to 2.24 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 169.2, 159.8, 141.7, 138.2, 137.7, 133.0, 129.7, 129.4, 128.3,, 127.8, 127.4, 124.7, 114.16, 92.5, 63.9, 55.41, 52.5, 44.4, 32.3, 20.1. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{22}H_{22}INO_4$ 491.0594; found 491.0590.



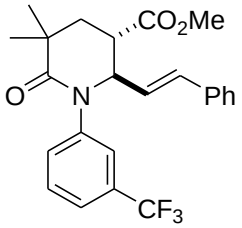
7f2

Prepared from imine **4b** (337 mg, 1.0 mmol) and 2,2-dimethyl glutaric anhydride (142 mg, 1.0 equiv), using General Procedures B and C. T = 110 ºC, time = 26 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 339 mg, 77% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 to 7.12 (7H, m), 6.84 to 6.81 (2H, d), 6.29 to 6.26 (1H, d), 5.91 to 5.87 (1H, dd), 4.75 to 4.70 (1H, t), 3.78 to 3.70 (6H, s,s), 3.03 to 2.98 (1H, m), 2.27 to 2.19 (1H, dd), 2.09 to 2.03 (1H, dd), 1.41 to 1.35 (6H, ss). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 173.2, 158.2, 136.0, 134.9, 134.3, 133.3, 129.3, 129.2, 128.7, 128.6, 128.2, 128.2, 128.1, 128.0, 126.6, 114.5, 64.7, 55.3, 52.1, 43.4, 38.4, 38.0, 28.4, 27.8. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{24}H_{27}NO_4$ 393.1940; found 393.1944.



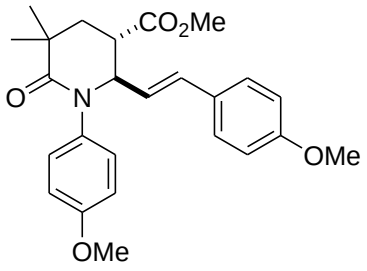
7g2

Prepared from imine **4c** (221 mg, 1.0 mmol) and 2,2-dimethyl glutaric anhydride (142 mg, 1.0 equiv), using General Procedures B and C. T = 110 ºC, time = 26 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 317 mg, 84% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.37 to 7.05 (9H, m), 6.29 to 6.25 (1H, d), 5.87 to 5.85 (1H, dd), 4.78 to 4.74 (1H, t), 3.77 (3H, s), 3.03 to 2.91 (1H, m), 2.36 to 2.26 (4H, m), 2.09 to 1.98 (1H, dd), 1.38 to 1.26 (6H, s,s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 173.2, 138.8, 136.7, 136.1, 133.3, 129.6, 129.4, 129.1, 128.5, 128.2, 127.9, 127.9, 127.2, 126.6, 126.5, 64.5, 51.9, 43.5, 38.0, 37.5, 29.3, 27.8, 20.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{24}H_{27}NO_3$ 377.1991; found 377.1995.



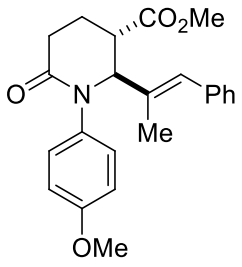
7h2

Prepared from imine **4e** (275 mg, 1.0 mmol) and 2,2-dimethyl glutaric anhydride (142 mg, 1.0 equiv), using General Procedures B and C. T = 110 ºC, time = 36 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 302 mg, 70% over 2 steps, 96:4 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 to 7.16 (9H, m), 6.33 (1H, d), 5.85 to 5.82 (1H, dd), 4.85 to 4.81 (1H, t), 3.70 (3H, s), 3.07 to 2.91 (1H, m), 2.27 to 2.22 (1H, dd), 2.09 to 2.01 (1H, dd), 1.46 (3H, s) 1.43 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 172.9, 142.0, 135.7, 134.3, 132.0, 131.4, 131.1, 129.4, 128.7, 128.6, 128.2, 127.4, 126.6, 126.4, 125.3, 125.2, 125.2, 125.2, 124.4, 64.6, 52.2, 43.3, 38.2, 37.4, 27.9. 27.3. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{24}H_{24}F_3NO_3$ 431.1708; found 431.1700.



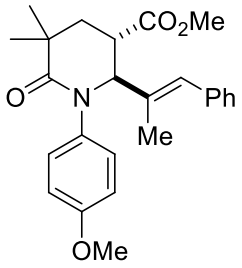
7i2

Prepared from imine **4f** (267 mg, 1.0 mmol) and 2,2-dimethyl glutaric anhydride (142 mg, 1.0 equiv), using General Procedures B and C. T = 105 ºC, time = 22 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 351 mg, 83% over 2 steps, 96:4 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 to 7.07 (4H, m), 6.83 to 6.77 (4H, m), 6.21 to 6.17 (1H, d), 5.76 to 5.70 (1H, dd), 4.71 to 4.67 (1H, t), 3.82 to 3.68 (9H, m), 3.01 to 2.96 (1H, m), 2.25 to 2.19 (1H, dd), 2.08 to 1.92 (1H, dd), 1.40 to 1.37 (6H, s,s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 173.3, 159.5, 158.1, 134.3, 132.8, 129.3, 129.0, 128.8, 128.6, 127.9, 127.7, 125.9, 114.6, 114.2, 114.0, 113.9, 64.8, 55.5, 55.3, 52.1, 43.6, 38.0, 37.5, 28.4, 28.0. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{25}H_{29}NO_5$ 423.2046; found 423.2051.



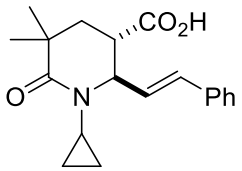
7j2

Prepared from imine **4i** (251 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. T = 105 ºC, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 300 mg, 79% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 to 7.12 (7H, m), 6.88 (2H, d), 6.43 (1H, s), 4.75 (1H, d), 3.77 to 3.66 (6H, s,s), 2.87 to 2.85 (1H, m), 2.71 to 2.58 (2H, m), 2.26 to 2.20 (2H, m), 1.80 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.0, 158.2, 136.8, 134.5, 129.7, 128.8, 128.4, 128.2, 126.9, 114.2, 69.6, 55.4, 52.4, 42.9, 30.4, 21.1, 15.3. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{23}H_{25}NO_4$ 379.1784; found 379.1789.



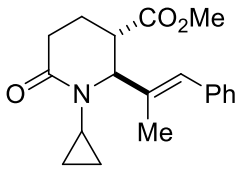
7k2

Prepared from imine **4i** (251 mg, 1.0 mmol) and 2,2-dimethyl glutaric anhydride (142 mg, 1.0 equiv), using General Procedures B and C. Temp = 110 °C, time = 36 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 300 mg, 79% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 to 7.09 (5H, m), 7.01 to 6.96 (2H, d), 6.78 to 6.74 (2H, d), 6.26 (1H, s), 4.68 (1H, d), 3.78 to 3.73 (6H, s,s), 3.22 to 3.16 (1H, m), 2.31 to 2.19 (1H, dd), 2.03 to 1.97 (1H, dd), 1.74 (3H, s), 1.43 (3H, s), 1.41 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 173.3, 159.3, 136.8, 134.2, 133.8, 132.9, 131.3, 131.2, 129.3, 129.0, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.1, 126.8, 114.5, 70.8, 55.4, 52.2, 41.78, 38.7, 38.1, 28.6, 28.2, 27.0, 13.7. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{25}H_{29}NO_4$ 407.2097; found 407.2093.



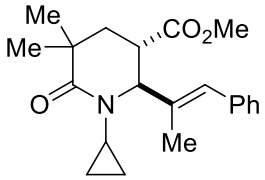
7i1

Prepared from imine **4k** (171 mg, 1.0 mmol) and 2,2-dimethyl glutaric anhydride (142 mg, 1.0 equiv), using General Procedures B and C. Temp = 100 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 235 mg, 75%, 98:2 dr. ^{1}H NMR (400 MHz, MeOH) δ 11.12 (1H, br. s), 7.42 to 7.22 (5H, m), 6.53 to 6.50 (1H, d), 6.22 to 6.16 (1H, dd), 4.50 to 4.48 (1H, t), 2.86 to 2.81 (1H, t), 2.57 to 2.48 (1H, t), 1.80 to 1.77 (2H, m), 1.26 to 0.53 (10H, m). ^{13}C NMR (101 MHz, MeOH) δ 179.1, 174.7, 136.2, 132.9, 128.3, 127.6, 126.2, 61.9, 48.2, 48.0, 48.0, 47.8, 47.8, 47.65, 47.5, 47.4, 47.3, 47.2, 47.1, 47.0, 42.3, 38.0, 36.0, 28.7, 27.3, 25.9, 9.34, 5.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{23}NO_3$ 313.1678; found 313.1683.



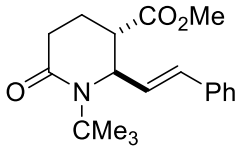
7m2

Prepared from imine **4l** (185 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. Temp = 100 ºC, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 226 mg, 72% over 2 steps, 98:2 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 to 7.13 (5H, m), 6.30 (1H, s), 4.36 to 4.33 (1H, d), 3.69 (3H, s), 2.88 to 2.80 (1H, dd), 2.54 to 2.30 (3H, m), 1.89 to 1.75 (5H, m), 0.96 to 0.91 (1H, m), 0.70 to 0.51 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 171.7, 136.8, 135.2, 129.1, 128.9, 128.4, 128.2, 128.2, 128.2, 128.1, 127.0, 126.9, 66.2, 51.9, 42.3, 30.4, 28.0, 20.1, 16.4, 8.8, 5.6. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{23}NO_3$ 313.1678; found 313.1683.



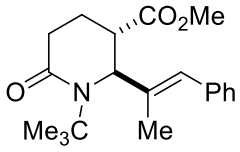
7n2

Prepared from imine **4l** (185 mg, 1.0 mmol) and 2,2-dimethyl glutaric anhydride (142 mg, 1.0 equiv), using General Procedures B and C. Temp = 100 ºC, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 239 mg, 70% over 2 steps, 98:2 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 to 7.21 (5H, m), 6.43 (1H, s), 4.37 (1H, d), 3.65 (3H, s),2.89 to 2.86 (1H, m), 2.36 to 2.31 (1H, t), 1.89 to 1.77 (5H, m), 1.32 to 1.25 (6H, s,s), 0.91 to 0.87 (1H, m), 0.70 to 0.55 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 173.6, 137.0, 135.0, 129.7, 128.9, 128.4, 128.3, 128.2, 126.9, 68.0, 52.1, 40.8, 38.3, 37.0, 28.5, 28.1, 26.4, 13.6, 9.8, 7.2. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{27}NO_3$ 341.1991; found 341.1995.



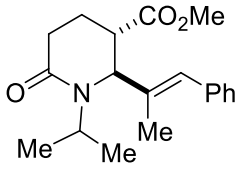
7o2

Prepared from imine **4n** (187 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. Temp = 100 °C, time = 12 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 258 mg, 82% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 to 7.14 (5H, m), 6.52 to 6.49 (1H, d), 6.19 to 6.07 (1H, dd), 5.03 to 5.01 (1H, dd), 3.78 (3H, s), 2.92 to 2.81 (1H, m), 2.53 to 2.31 (2H, m), 2.15 to 1.90 (2H, m), 1.47 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 170.6, 136.0, 133.2, 129.1, 128.7, 128.1, 127.9, 126.4, 58.7, 58.2, 51.6, 44.7, 31.0, 28.5, 18.6. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{25}NO_3$ 315.1834; found 315.1839.



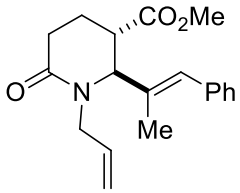
7p2

Prepared from imine **4o** (201 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. Temp = 100 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 250.0 mg, 76% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 to 7.17 (5H, m), 6.39 (1H, s), 4.71 (1H, d), 3.76 (3H, s), 2.92 to 2.88 (1H, m), 2.55 to 2.32 (3H, m), 2.23 to 1.82 (4H, m), 1.49 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 170.5, 136.9, 129.0, 128.8, 128.2, 127.6, 127.2, 126.9, 62.3, 58.6, 55.3, 41.7, 31.1, 28.8, 19.4, 17.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{20}H_{27}NO_3$ 329.1991; found 329.1995.



7q2

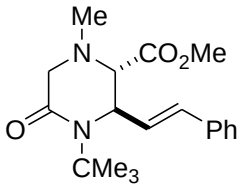
Prepared from imine **4q** (187 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. Temp = 100 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 239.6 mg, 76% over 2 steps, 90:10 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 to 7.21 (5H, m), 6.39 (1H, s), 4.55 to 4.37 (2H, m), 3.77 (3H, s), 2.88 to 2.82 (1H, m), 2.63 to 2.37 (2H, m), 2.08 to 1.76 (5H, m), 1.41 to 1.26 (6H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.82, 170.14, 137.03, 136.84, 136.42, 129.88, 128.87, 127.88, 126.98, 125.56, 61.80, 55.02, 47.93, 41.67, 30.38, 20.95, 20.16, 19.52, 18.86. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{25}NO_3$ 315.1834; found 315.1839.



7r2

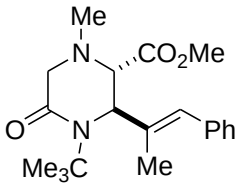
Prepared from imine **4v** (185 mg, 1.0 mmol) and glutaric anhydride (114 mg, 1.0 equiv), using General Procedures B and C. Temp = 100 °C, time = 18 h. Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50 to 0:100). Yield = 235 mg, 75% over 2 steps, 95:5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 to 7.02 (5H, m), 6.34 (1H, s), 5.82 to 5.72 (1H, m), 5.13 to 5.05 (2H, m), 4.75 to 4.70 (1H, dd), 4.38 (1H, d), 3.72 to 3.60 (4H, m), 3.28 to 3.21 (1H, dd), 2.87 to 2.80 (1H, m), 2.49 to 2.20 (2H, m), 2.03 to 1.69 (5H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 169.6, 136.7, 134.4, 132.7, 129.1, 128.9, 128.3, 127.0, 118.0, 65.2, 52.2, 46.3, 42.6, 30.1, 21.0, 16.1. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{19}H_{23}NO_3$ 313.1678; found 313.1684.

S2-5: Hexannelation of 1,3-azadienes with 4-methylmorpholine-2,6-dione



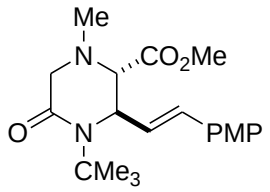
8a2

Prepared from 4-methylmorpholine-2,6-dione (129 mg, 1.0 equiv) using General Procedures B & C. T = 100 °C, time = 24 h. Yield = 290.8 mg, 88%. ^{1}H NMR (400 MHz, CDCl3) δ 7.36 (d, *J* = 7.0 Hz, 2H), 7.28 (dt, *J* = 14.9, 7.6 Hz, 3H), 7.21 (d, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.28 (dd, *J* = 16.0, 7.3 Hz, 1H), 4.69 (dd, *J* = 7.7, 2.8 Hz, 1H), 3.73 (s, 3H), 3.62 to 3.49 (m, 3H), 2.44 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 168.0, 136.2, 131.4, 130.9, 130.2, 130.0, 129.2, 128.7, 128.1, 128.0, 126.6, 126.0, 67.1, 58.3, 58.1, 55.6, 51.7, 41.7, 28.4. **HRMS-EI+** (*m/z*): calc'd for $C_{19}H_{26}N_2O_3$ 330.1943; found 330.4213.



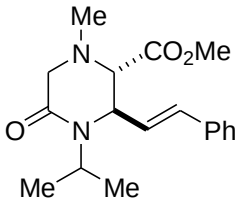
8b2

Prepared from 4-methylmorpholine-2,6-dione (129 mg, 1.0 equiv) using General Procedures B & C. T = 100 °C, time = 24 h. Yield = 285.9 mg, 83%. ^{1}H NMR (400 MHz, CDCl3) δ 7.51 (d, *J* = 7.5 Hz, 1H), 7.47 to 7.16 (m, 4H), 6.40 (s, 1H), 4.52 (s, 1H), 3.74 (s, 3H), 3.64 to 3.41 (m, 1H), 2.44 (s, 2H), 1.94 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 168.6, 137.3, 130.0, 129.6, 129.3, 129.0, 128.8, 128.5, 128.3, 127.8, 127.4, 127.0, 126.8, 65.1, 63.3, 58.4, 55.7, 51.7, 41.8, 27.9, 16.1. **HRMS-EI+** (*m/z*): calc'd for $C_{20}H_{28}N_2O_3$ 344.2100; found 344.4479.



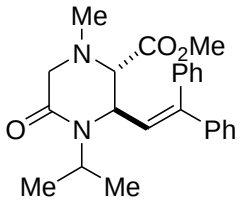
8c2

Prepared from 4-methylmorpholine-2,6-dione (129 mg, 1.0 equiv) using General Procedures B & C. T = 100 ºC, time = 24 h. Yield = 287.9 mg, 79%. ^{1}H NMR (400 MHz, CDCl3) δ 7.30 (m, 2H), 6.93 to 6.72 (m, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.13 (dd, *J* = 16.0, 7.5 Hz, 1H), 4.66 (dd, *J* = 7.5, 2.6 Hz, 1H), 3.87 to 3.64 (m, 8H), 3.50 (dt, *J* = 29.0, 17.1 Hz, 3H), 2.44 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 168.0, 159.5, 130.8, 130.3, 129.0, 128.6, 128.0, 127.8, 114.1, 67.2, 58.3, 58.0, 55.6, 55.4, 51.6, 41.7, 28.4. **HRMS-EI+** (*m/z*): calc'd for $C_{20}H_{28}N_2O_4$ 360.2049; found 360.4473.



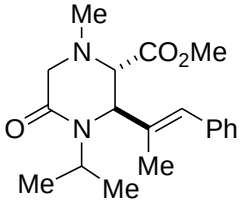
8d2

Prepared from 4-methylmorpholine-2,6-dione (129 mg, 1.0 equiv) using General Procedures B & C. T = 100 ºC, time = 24 h. Yield = 268.9 mg, 85%. ^{1}H NMR (400 MHz, CDCl3) δ 7.43 to 7.12 (m, 5H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.33 (dd, *J* = 16.0, 7.9 Hz, 1H), 4.52 (h, *J* = 7.1 Hz, 1H), 4.34 (d, *J* = 7.7 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 3.62 to 3.42 (m, 2H), 2.44 (s, 3H), 1.16 (dt, *J* = 40.7, 6.7 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 166.8, 136.2, 131.7, 130.5, 129.8, 129.0, 128.7, 128.2, 128.1, 126.9, 66.6, 57.4, 54.5, 51.7, 46.5, 46.1, 42.1, 21.1, 20.6, 19.7. **HRMS-EI+** (*m/z*): calc'd for $C_{18}H_{24}N_2O_3$ 316.1787; found 316.3948.



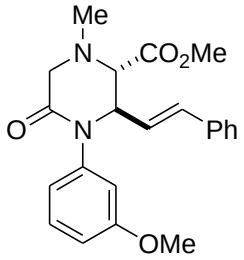
8e2

Prepared from 4-methylmorpholine-2,6-dione (129 mg, 1.0 equiv) using General Procedures B & C. T = 100 ºC, time = 24 h. Yield = 306.2 mg, 78%. ^{1}H NMR (400 MHz, CDCl3) δ 7.41 (dt, *J* = 13.6, 7.1 Hz, 4H), 7.29 to 7.15 (m, 8H), 6.27 (d, *J* = 9.4 Hz, 1H), 4.47 (h, *J* = 9.3, 8.1 Hz, 1H), 4.36 (d, *J* = 9.4 Hz, 1H), 3.63 (d, *J* = 16.2 Hz, 3H), 3.53 (d, *J* = 17.3 Hz, 3H), 2.49 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 166.6, 142.3, 141.5, 138.8, 130.1, 130.0, 129.7, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 66.6, 54.5, 54.2, 53.4, 51.8, 51.6, 45.7, 42.2, 20.7, 19.1. **HRMS-EI+** (*m/z*): calc'd for $C_{24}H_{28}N_2O_3$ 392.2100; found 392.4907.



8f2

Prepared from 4-methylmorpholine-2,6-dione (129 mg, 1.0 equiv) using General Procedures B & C. T = 100 ºC, time = 24 h. Yield = 267.6 mg, 81%. ^{1}H NMR (400 MHz, CDCl3) δ 7.34 (p, *J* = 6.8, 5.5 Hz, 3H), 7.29 to 7.18 (m, 3H), 6.43 (s, 1H), 4.67 to 4.50 (m, 1H), 4.27 to 4.21 (m, 1H), 3.73 (s, 3H), 3.71 to 3.54 (m, 2H), 3.54 to 3.35 (m, 1H), 2.46 (d, *J* = 16.5 Hz, 3H), 1.95 (d, *J* = 6.1 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 167.7, 137.7, 137.5, 137.2, 129.8, 129.0, 128.90, 128.7, 128.5, 128.3, 128.1, 127.0, 126.8, 65.5, 62.1, 54.6, 54.3, 53.7, 52.1, 51.8, 51.6, 46.5, 45.9, 43.3, 42.0, 41.8, 29.76, 20.0, 19.8, 19.4, 18.8. **HRMS-EI+** (*m/z*): calc'd for $C_{19}H_{26}N_2O_3$ 330.1943; found 330.4213.



8g2

Prepared from 4-methylmorpholine-2,6-dione (129 mg, 1.0 equiv) using General Procedures B & C. T = 100 °C, time = 24 h. Yield = 266.3 mg, 70%. ^{1}H NMR (400 MHz, CDCl3) δ 7.37 to 7.25 (m, 4H), 7.29 to 7.15 (m, 2H), 6.92 to 6.72 (m, 2H), 6.72 (t, *J* = 2.3 Hz, 1H), 6.44 (dd, *J* = 15.9, 8.2 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 4.59 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.83 (s, 3H), 3.71 (d, *J* = 9.9 Hz, 4H), 3.67 to 3.57 (m, 2H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 166.7, 160.2, 141.9, 136.0, 133.6, 130.2, 130.0, 129.7, 129.1, 128.7, 128.2, 127.2, 126.8, 126.7, 120.0, 113.5, 66.0, 64.9, 55.6, 55.3, 54.9, 52.0, 42.6. **HRMS-EI+** (*m/z*): calc'd for $C_{22}H_{24}N_2O_4$ 380.1736; found 380.4370.

CHAPTER 3

SYNTHETIC APPLICATIONS OF ALLYLIC LACTAMOYL ESTERS

Access to a highly functionalized and diastereoselective common intermediate is the ultimate goal as a DOS strategy. Reaching this intermediate can allow access to various motifs through further functionalizations. Through the modular and cost-effective synthesis of our allylic lactamoyl acid/ester **1**, we envision being able to synthesize polycyclic motifs **2-9** through various cyclization methods as seen in Figure 3-1.

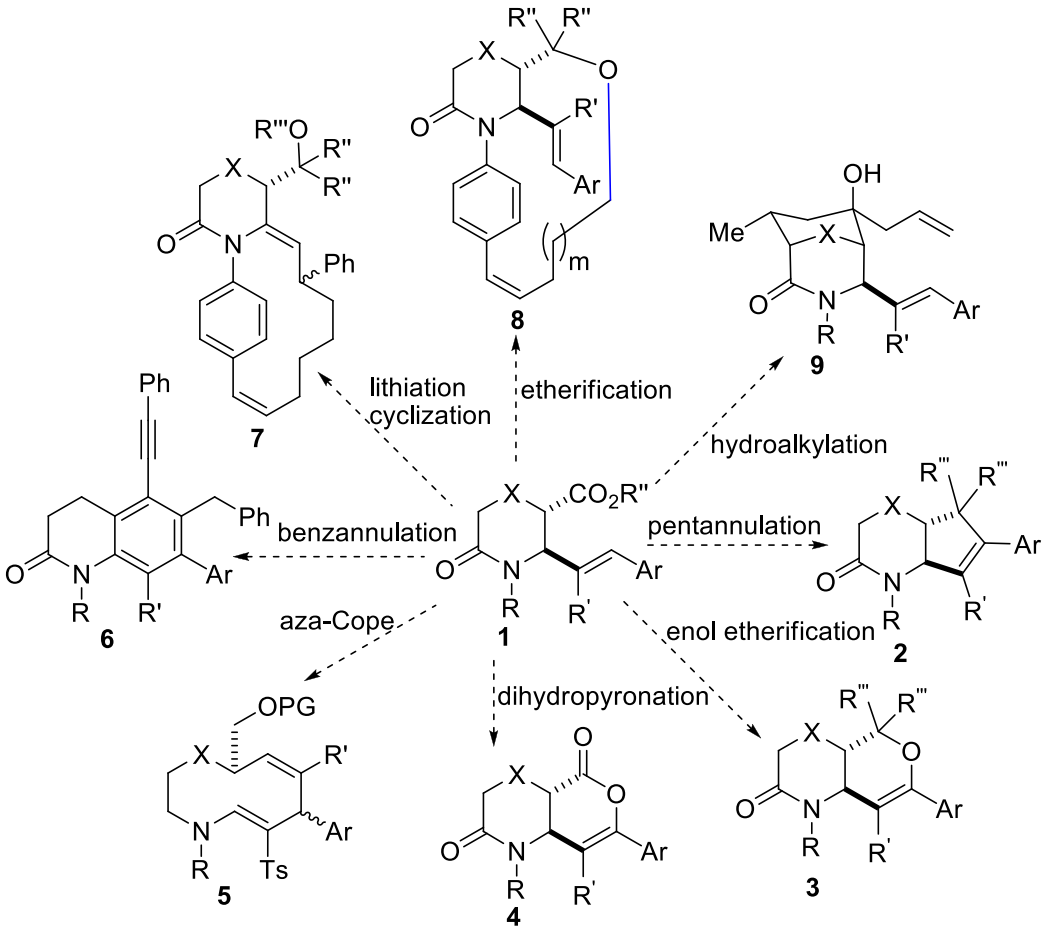
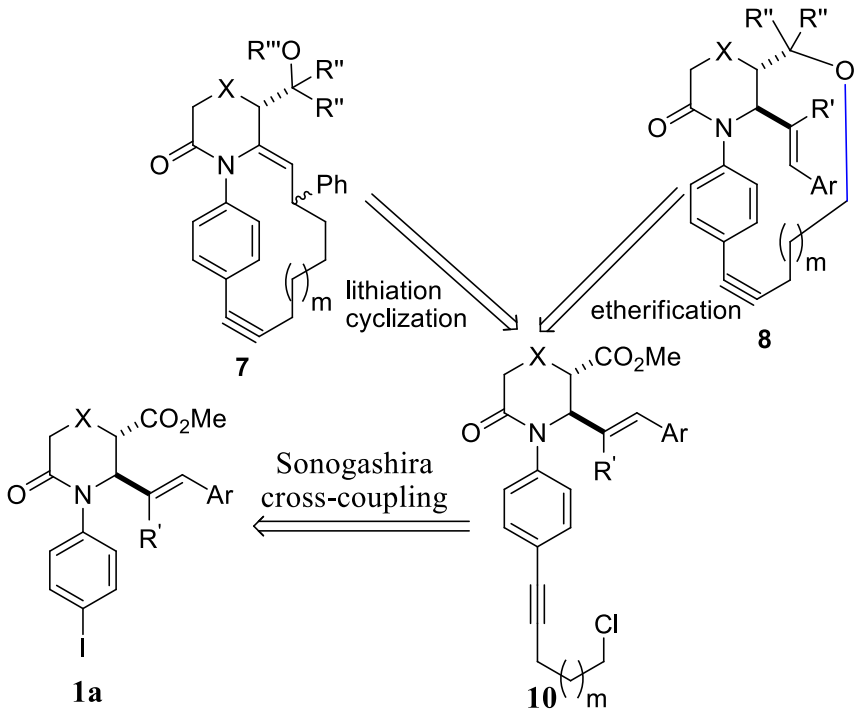


Figure 3-1. Synthetic potential of versatile intermediate **1**.

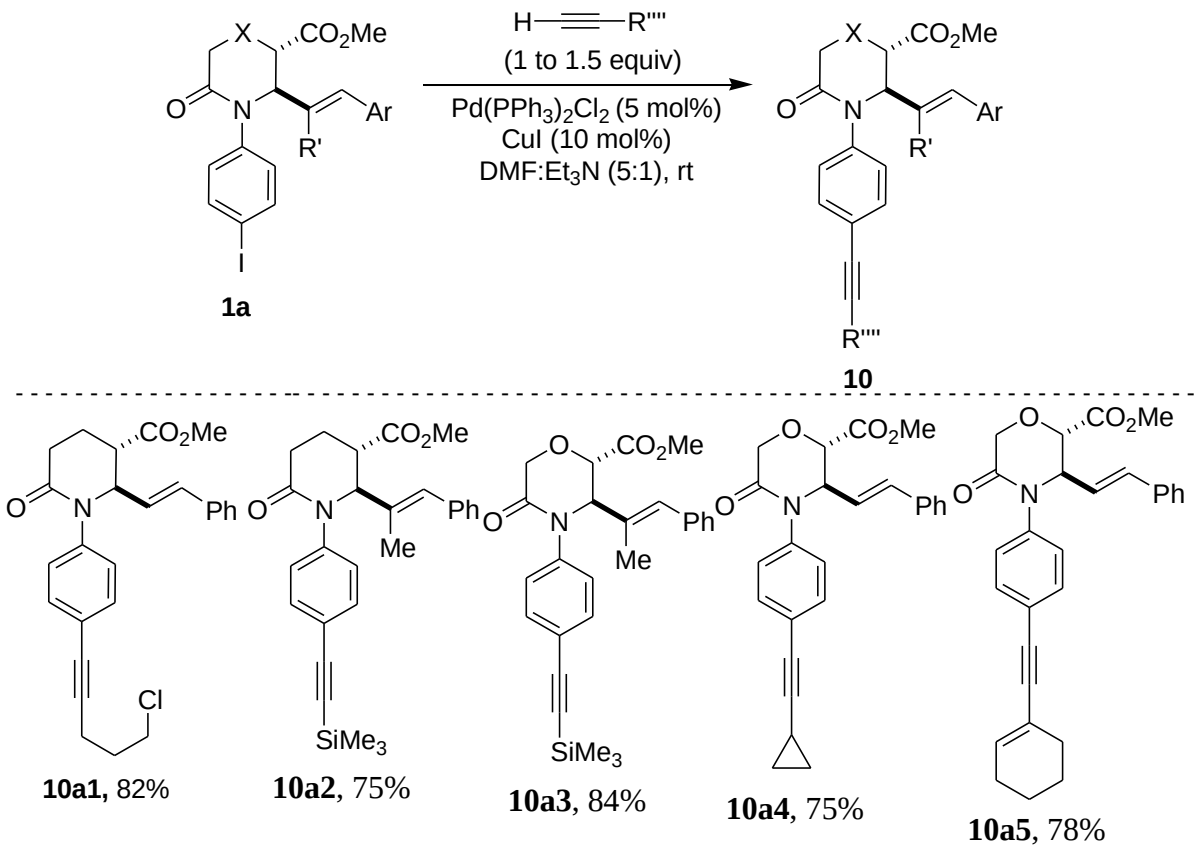
3.1: Progress toward the synthesis of macrocyclic enamidynes

Macrocycles are eight or more membered ring systems, some of which constitute the core of pharmaceuticals and natural products. Due to their large size and multiple positions for functionalization, the synthesis of these macrocycles have become one of the most expansive fields in synthetic chemistry. However, macrocycles tend to be unstable due to the large size allowing for expanding and contracting of bonds. Additionally, their construction from acylic precursors can be rendered difficult due to high entropic and enthalpic costs. Indeed, common approaches to functionalized *N*-macrocycles such as rhazilinam almost always fearing a ring-closing metathesis step. Herein, we propose a synthesis of novel macrocyclic enamidynes **7/8** that utilizes in-house allylic lactamoyl esters of type **1** (Scheme 3-1). It is theorized that Sonagashira cross-coupling of iodoarylated lactam **1a** with terminal alkynes, which bear a pendant leaving group would afford **10**. Subsequent lithiation-cyclization of Williamson-etherification of **10** would set the stage for accessing **7** and **11**, respectively. It is recognized that geometrical constraints could prevent macrocyclization. In that scenario, the reduction of the alkyne to alkene would be effected.



Scheme 3-1. Synthetic approach to macrocyclic enamidynes.

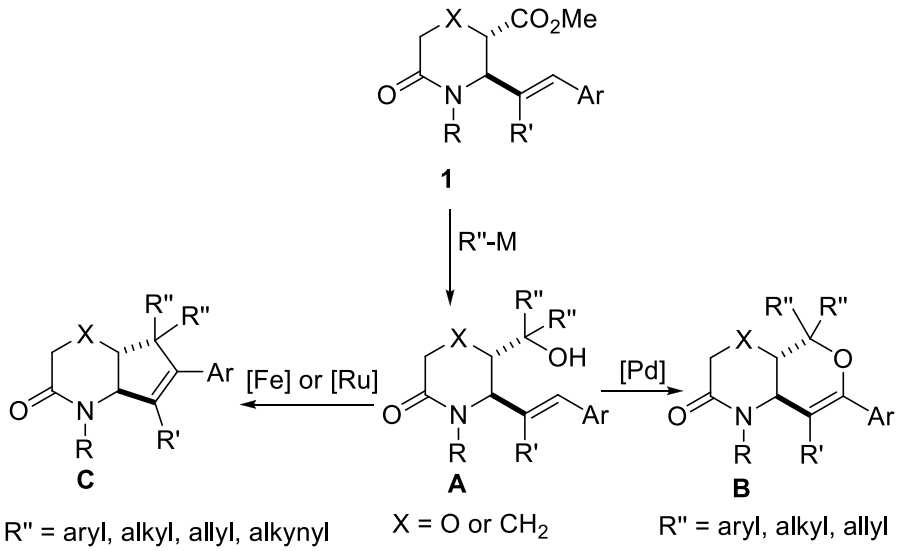
Studies toward the assembly of the proposed macrocyclic architectures began with attempts to successfully couple **1a** and terminal alkynes using conditions developed by another graduate student in our group (on a different substrate). In the event, it was found that coupling of iodoarylated lactams with electronically diverse alkynes, under palladium and copper catalyst proceeded satisfactorily and delivered the internal alkynes depicted in Scheme 3-2. These compounds are currently being advanced to the proposed macrocycles.



Scheme 3-2. Sonogashira cross-coupling of *para*-iodoarylated lactams.

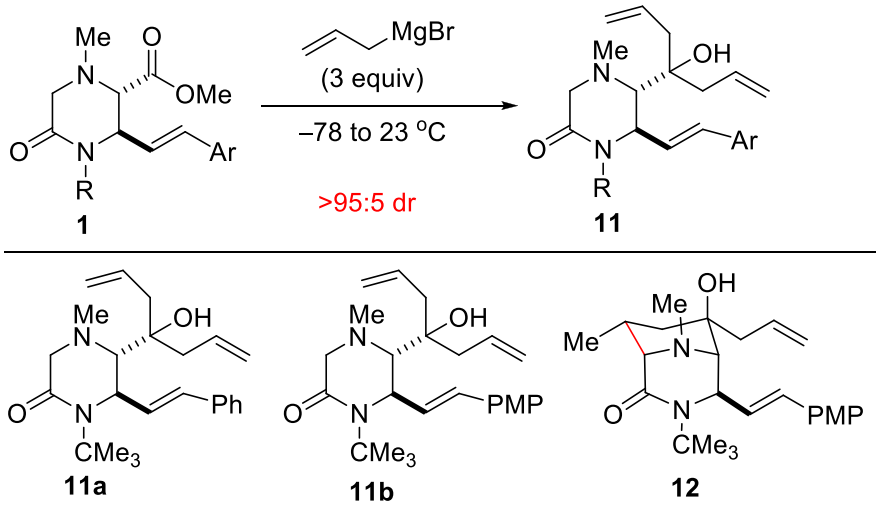
3.2: Regio- and diasteroselective one-pot hydro(amino)alkylation of lactamoyl esters

During the course of these studies, we found that lactamoyl esters of type **1** can react chemoselectively with organometallic reagents to afford tertiary alcohols such as **A**,[193] which were subsequently converted to bicyclic motifs such as **B** and **C** by other researchers in our group (Scheme 3-3).[194]



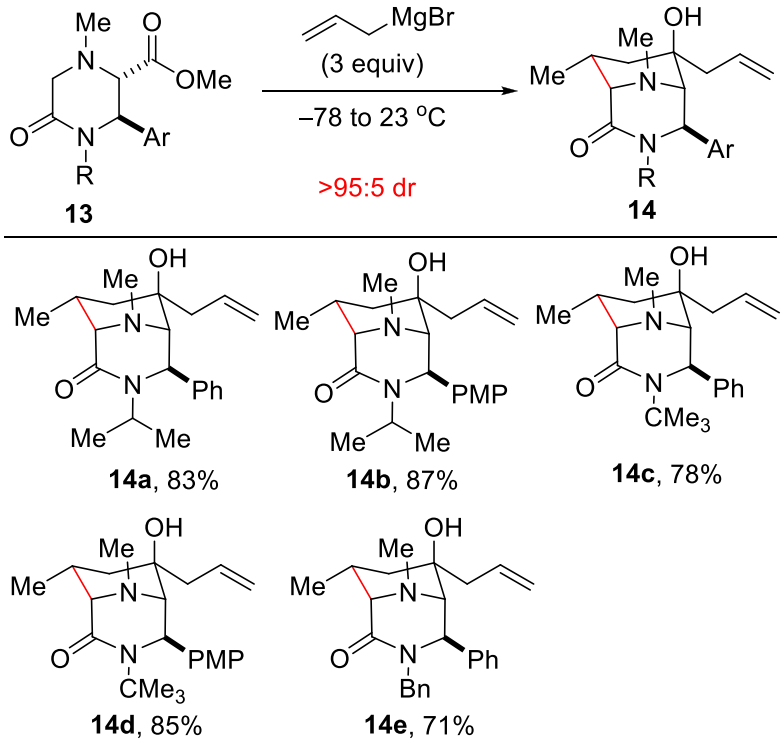
Scheme 3-3. Previous work from our group on chemoselective addition of organometallic reagents to lactamoyl esters.

Attempts to extend this mode of reactivity to piperazinonates have led to the surprising but exciting discovery that in the presence of excess allylmagnesium bromide, diastereoselective formation of bicycles of type **12** (Scheme 3-4) is achievable.



Scheme 3-4. Preliminary evidence for the hydroaminoalkylation of **1**

Optimization results have since revealed that the reaction works better when the C2 substituent is an aryl group rather than a vinyl groups (Scheme 3-5). The reason for this is not clear at this point. Nonetheless, this groundbreaking result highlights the first example of hydroaminoalkylation in the absence of a transition metal. The reaction takes place with branced regioselectivity and the diastereoselectivity is impeccable. During the process, three new stereocenters are created with complete stereocontrol. The relative configuration of the product is not fully established at this point.



Scheme 3-5. Hydroaminoalkylation of benzylic lactamoyl esters

Our mechanistic hypothesis is presented in Figure 3-2. Reaction of two equivalents of allylmagnesium bromide with **13** delivers a tertiary alkoxide, while a third equivalent of the Grignard reagents enolizes the amide motif, giving rise to **15**. Subsequent intramolecular

hydroalkylation affords intermediate **16**, which gets protonated during workup to afford bicycle **14**.

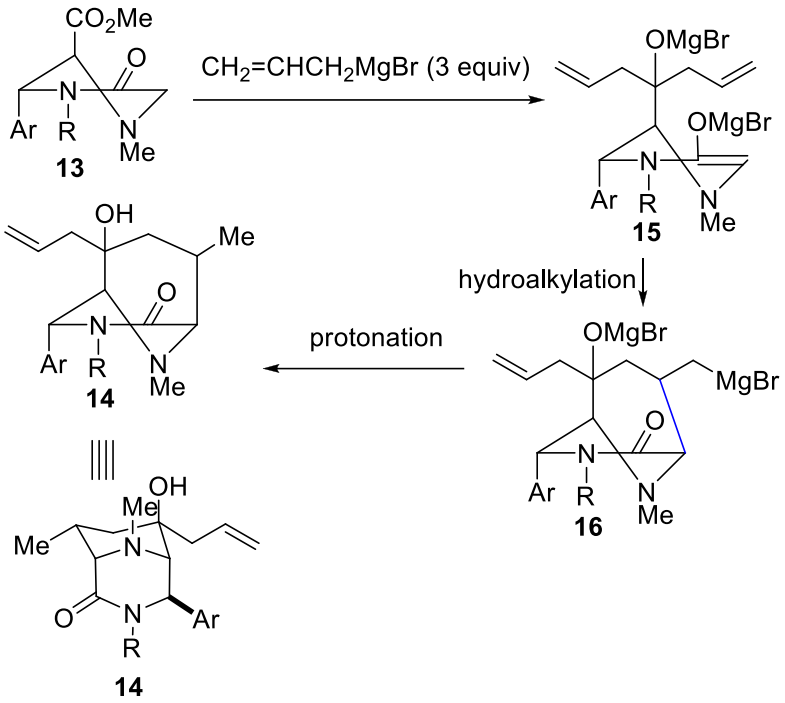


Figure 3-2. Mechanistic rationale for hydroalkylation of **13**.

The possibility exists that the reaction proceeds via metallaazirindine **18** followed by olefin insertion and protonative workup (Figure 3-3), but we are unsure at this point.

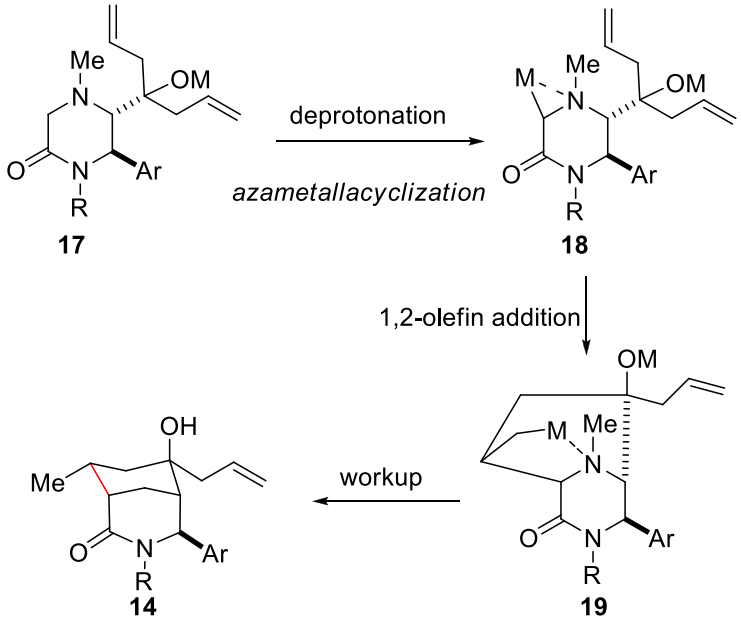


Figure 3-3. Alternative mechanistic rationale for hydroaminoalkylation of **13**.

3.3: Conclusion

The synthetic utility of the cycloadducts prepared using methodology derived herein has been exemplified through the achievement of some sagacious cross-coupling events, which have paved the way for eventual construction of alkyne-bearing N-macrocycles. Importantly, we have found an unprecedented example of a hydroamino alkylation that is transition metal-free and occurs at room temperature. Details of the transformation are being fletched out by some other members of the group.

S3: Supporting Information for Chapter 3

S3-1: General Experimental Information and Procedures

All experiments involving air and moisture sensitive reagents, such as palladium precatalysts and organolithium reagents, were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 µm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ stain. Unless otherwise indicated, ^1H, ^{13}C, and DEPT-135 NMR, COSY 45, HMQC, and NOESY spectra were acquired using DMSO-d_6, CD_3OD or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^+ data were obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).

General Procedure D: Sonogashira cross-coupling with iodoarylated lactams

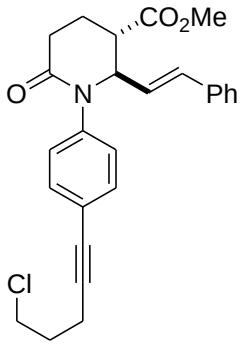
To the crude lactamoyl ester (1.0 mmol) dissolved in Et_3N:DMF (1:5 mL) was added $Pd(PPh_3)_2Cl_2$ (5 mol%) and copper iodine (5 mol%) under nitrogen atmosphere. After initial mixing, 5-chloro-1-pentyne (1.1 mmol) is injected. The reaction mixture was stirred for 12 to 24 h (TLC monitoring). After complete conversion, it was diluted with water and extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired alkynyl-arylated lactam. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (1:2).

General Procedure E: Grignard Additon

To the crude lactamoyl ester (1.0 mmol) dissolved in freshly distilled THF (5 mL), was slowly added methyl magnesium bromide (2.0 mL, 1.0 M solution in THF, 3 equiv) under nitrogen at –78 °C. After complete consumption of the ester (as indicated by TLC and GC-MS), the mixture quenched by slow addition of *sat.* aq NH_4Cl. The mixture was diluted with Et_2O.

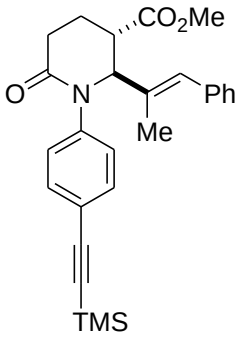
The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 for 30 min, filtered, and concentrated under reduced pressure to give the desired product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (1:2).

S3-2: Songashira Cross-Coupling with iodoarylated lactamoyl esters



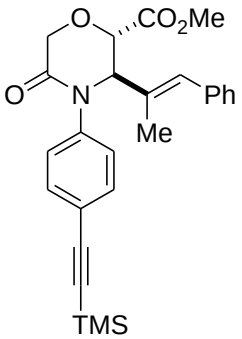
10a

Prepped from aryl iodide **7d2** (461 mg, 1 mmol, 1.0 equiv) and 5-chloro-1-pentyne (0.212 mL, 2 mmol, 2 equiv), using General Procedure D. Yield = 356.9 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 to 7.16 (9H, m), 6.41 to 6.37 (1H, d), 6.18 to 6.06 (1H, dd), 4.89 to 4.86 (1H, dd), 3.78 to 3.63 (5H, m), 2.93 to 2.86 (2H, m), 2.65 to 2.51 (4H, m), 2.34 to 2.18 (2H, m), 2.03 to 1.97 (2H, m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 169.2, 141.3, 135.7, 134.9, 133.4, 132.3, 128.7, 128.4, 127.5, 127.3, 126.7, 124.3, 122.5, 88.7, 81.1, 63.6, 52.5, 44.7, 43.8, 31.4, 29.7, 21.1, 16.9. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{26}H_{26}ClNO_3$ 435.1601; found 435.1609.



10a2

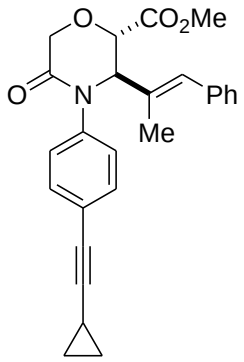
Prepped from α-methyl derivative of aryl iodide **7d2** (475 mg, 1 mmol, 1.0 equiv) and ethynyltrimethylsilane (0.277 mL, 2 mmol, 2 equiv), using General Procedure D. Yield = 334.2 mg, 75%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.32 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (dd, *J* = 7.7, 5.6 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 6.41 (s, 1H), 4.79 (d, *J* = 5.7 Hz, 1H), 3.76 (s, 3H), 3.67 (d, *J* = 9.4 Hz, 1H), 3.06 – 2.92 (m, 1H), 2.75 – 2.55 (m, 1H), 2.41 (dt, *J* = 15.4, 7.1 Hz, 1H), 2.24 (dtt, *J* = 9.3, 6.7, 3.2 Hz, 1H), 1.92 – 1.77 (m, 2H), 0.23 (d, *J* = 4.4 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 169.7, 141.8, 136.6, 134.3, 132.7, 130.0, 129.0, 128.8, 128.6, 128.3, 127.6, 127.3, 127.1, 121.8, 104.6, 94.7, 69.1, 52.5, 42.8, 30.5, 21.0, 20.6, 15.3, 0.1. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{27}H_{31}NO_3Si$ 445.2073; found 445.6254.



10a3

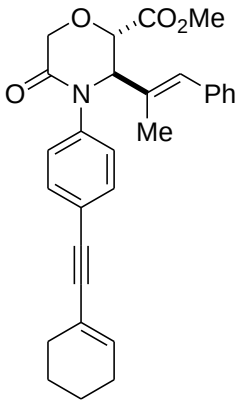
Prepped from aryl iodide made by coworker (477 mg, 1 mmol, 1.0 equiv) and ethynyltrimethylsilane (0.277 mL, 2 mmol, 2 equiv), using General Procedure D. Yield = 376.0 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.41 (m, 2H), 7.31 (q, *J* = 7.3 Hz, 2H), 7.24 (d, *J* = 6.3 Hz, 3H), 7.18 – 7.08 (m, 2H), 6.45 (s, 1H), 4.79 (d, *J* = 3.4 Hz, 1H), 4.74 – 4.62

(m, 2H), 4.45 (d, *J* = 17.3 Hz, 1H), 3.85 (s, 3H), 1.93 (s, 3H), 0.25 (d, *J* = 5.1 Hz, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 166.2, 139.8, 136.3, 132.9, 132.8, 130.7, 129.0, 128.4, 128.3, 127.3, 126.3, 104.3, 95.2, 75.0, 67.6, 65.7, 53.0, 15.0, 0.1. **HRMS-EI**$^+$ (*m/z*): calc'd for $C_{26}H_{29}NO_4Si$ 447.1866; found 447.5983.



10a4

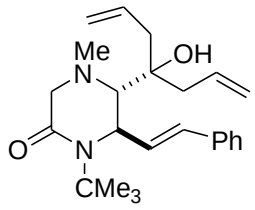
Prepped from aryl iodide made by coworker (477 mg, 1 mmol, 1.0 equiv) and cyclopropylacetlene (0.2 mL, 2 mmol, 2 equiv) using General Procedure D. Yield = 249.3 mg, 75%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (td, *J* = 19.4, 18.3, 6.9 Hz, 7H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.28 (dd, *J* = 15.8, 7.9 Hz, 1H), 4.80 (dd, *J* = 8.0, 2.7 Hz, 1H), 4.69 (d, *J* = 17.3 Hz, 1H), 4.57 (d, *J* = 2.7 Hz, 1H), 4.52 – 4.41 (m, 1H), 3.86 (s, 2H), 3.78 (d, *J* = 14.3 Hz, 1H), 1.42 (tt, *J* = 8.8, 5.0 Hz, 1H), 0.92 – 0.73 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 165.6, 138.9, 135.4, 134.7, 132.6, 128.8, 128.6, 126.7, 124.5, 94.5, 75.8, 75.1, 72.10,65.5, 63.1, 53.0, 8.7, 0.2. **HRMS-EI**$^+$ (*m/z*): calc'd for $C_{26}H_{25}NO_4$ 415.1784; found 415.4810.



10a5

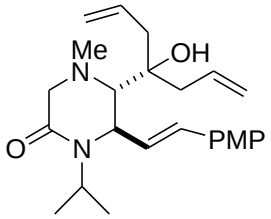
Prepped from aryl iodide made by coworker (477 mg, 1 mmol, 1.0 equiv) and 1-ethynylcyclohexene (0.2 mL, 2 mmol, 2 equiv), using General Procedure D. Yield = 355.3 mg, 76%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 8.1 Hz, 3H), 7.29 (d, *J* = 14.0 Hz, 3H), 7.27 – 7.15 (m, 3H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.29 (dd, *J* = 15.8, 7.8 Hz, 1H), 6.20 (q, *J* = 5.7, 4.1 Hz, 1H), 4.85 – 4.78 (m, 1H), 4.69 (d, *J* = 17.2 Hz, 1H), 4.58 (d, *J* = 2.7 Hz, 1H), 4.46 (d, *J* = 17.3 Hz, 1H), 3.83 (s, 3H), 2.23 – 2.07 (m, 4H), 1.70 – 1.53 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 165.7, 139.2, 135.9, 135.7, 134.6, 132.4, 132.3, 128.8, 128.6, 126.7, 124.6, 120.6, 92.2, 86.1, 75.7, 65.5, 63.1, 52.9, 29.2, 25.8, 22.4, 21.6. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{29}H_{29}NO_4$ 455.2097; found 455.5449.

S3-3: Allylic Grignard Addition to lactamoyl esters



11a

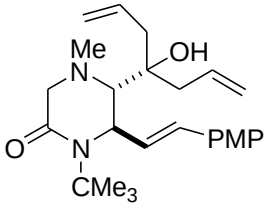
Prepped from allylic ketopiperazine **8a2** (330.2 mg, 1 mmol, 1.0 equiv) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Preliminary data. ^{1}H NMR (400 MHz, CDCl3) δ 7.33 to 7.28 (m, 5H), 6.50 (d, *J* = 16.0, 1H), 6.12 (dd, *J* = 16.0, 6.5 Hz, 1H), 6.03 to 5.83 (m, 2H), 5.22 to 5.09 (m, 4H), 4.69 (d, *J* = 6.5 Hz, 1H), 3.64 (d, *J* = 15.8 Hz, 1H), 3.34 (d, *J* = 15.8 Hz, 1H), 2.80 (s, 1H), 2.50 to 2.20 (m, 8H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 136.2, 134.3, 134.2, 133.7, 132.7, 131.7, 131.1, 130.8, 130.3, 128.8, 128.6, 128.1, 127.7, 127.2, 126.6, 126.5, 126.4, 125.6, 118.7, 118.4, 76.4, 69.3, 58.9, 58.2, 55.3, 48.3, 41.5, 41.3, 28.5. **HRMS-EI^{+}** (*m/z*): calc'd for $C_{24}H_{34}N_2O_2$ 382.2620; found 382.5390.



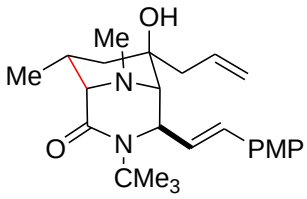
11b

Prepped from allylic ketopiperazine **8d2** (346.2 mg, 1 mmol, 1.0 equiv) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Preliminary data. ^{1}H NMR (400 MHz, CDCl3) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.02 (dd, *J* = 15.9, 7.2 Hz, 1H), 5.90 (tq, *J* = 16.5, 7.7 Hz, 2H), 5.14 (td, *J* = 17.0, 15.4, 7.9 Hz, 4H), 4.48 (dq, *J* = 13.5, 6.8 Hz, 1H), 4.40 (d, *J* = 7.3 Hz, 1H), 3.81 (s, 4H), 3.31 (d, *J* = 16.7 Hz, 1H), 2.80 (s, 1H), 2.62 (s, 3H), 2.33 (dddd, *J* = 59.9, 27.3, 14.2, 7.3 Hz, 5H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.23 (q, *J* = 7.2, 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 159.6, 134.1, 133.6, 130.2, 129.1, 128.9, 128.6, 127.9, 127.8, 118.9, 118.7,

118.5, 114.2, 68.7, 56.6, 55.4, 54.8, 48.2, 47.9, 47.8, 41.8, 41.5, 41.1, 21.1, 20.8, 20.1. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{24}H_{34}N_2O_3$ 398.2569; found 398.5384.

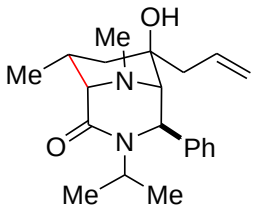


11c



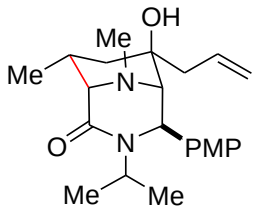
12

Prepped from allylic ketopiperazine **8c2** (360.2 mg, 1 mmol, 1.0 equiv) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Complex mixture limited spectral data.



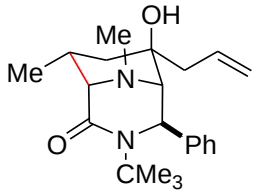
13a

Prepped from aryl ketopiperazine (290.2 mg, 1 mmol, 1.0 equiv. made via General Procedure A-C) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Yield = 284.3 mg, 83%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.19 (m, 5H), 6.01 (tt, *J* = 17.2, 7.3 Hz, 1H), 5.28 – 5.18 (m, 2H), 4.35 (s, 1H), 3.78 (s, 1H), 3.39 (h, *J* = 6.7 Hz, 1H), 3.11 (d, *J* = 4.6 Hz, 1H), 2.75 (s, 1H), 2.54 (s, 3H), 2.51 – 2.41 (m, 1H), 2.30 (dt, *J* = 13.6, 6.3 Hz, 1H), 1.67 (dd, *J* = 13.9, 4.1 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H), 1.30 – 1.15 (m, 4H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 143.0, 133.0, 128.5, 127.4, 127.3, 118.8, 72.3, 68.7, 65.5, 60.4, 52.6, 44.3, 43.5, 38.6, 29.7, 21.3, 19.4, 18.2. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{21}H_{30}N_2O_2$ 342.2307; found 342.4751.



13b

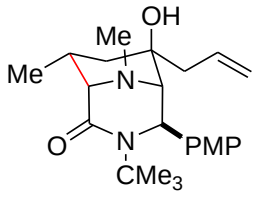
Prepped from aryl ketopiperazine (320.2 mg, 1 mmol, 1.0 equiv. made via General Procedure A-C) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Yield = 324.1 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (s, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.01 (dq, *J* = 16.4, 7.6 Hz, 1H), 5.35 – 5.27 (m, 1H), 5.28 – 5.19 (m, 1H), 4.32 (s, 1H), 3.80 (s, 3H), 3.43 (dq, *J* = 13.6, 7.2 Hz, 1H), 3.13 (d, *J* = 4.8 Hz, 1H), 2.74 (s, 1H), 2.57 (s, 3H), 2.48 (t, *J* = 6.2 Hz, 2H), 2.31 (dt, *J* = 12.4, 6.3 Hz, 1H), 1.67 (dd, *J* = 13.9, 4.2 Hz, 2H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.30 – 1.14 (m, 5H), 1.01 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 158.7, 134.8, 132.9, 128.5, 118.8, 113.9, 72.3, 68.8, 65.5, 59.9, 55.3, 52.5, 44.4, 43.4, 38.6, 29.8, 21.2, 19.4, 18.2. **HRMS-EI**$^{+}$ (*m/z*): calc'd for $C_{22}H_{32}N_2O_3$ 372.2413; found 372.5011.



13c

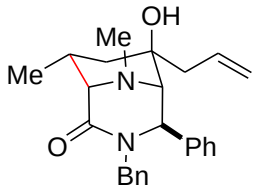
Prepped from aryl ketopiperazine (304.4 mg, 1 mmol, 1.0 equiv. made via General Procedure A-C) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Yield = 278.1 mg, 78%. ^{1}H NMR (400 MHz, CDCl3) δ 7.34 (d, *J* = 7.7 Hz, 2H), 7.32 to 7.17 (m, 3H), 6.18 to 6.02 (m, 1H), 5.35 to 5.24 (m, 2H), 3.42 (s, 1H), 3.13 (d, *J* = 4.3 Hz, 1H), 2.71 (s, 1H), 2.49 (td, *J* = 14.2, 6.9 Hz, 2H), 2.42 (s, 3H), 2.37 to 2.29 (m, 1H), 1.66 (dd, *J* = 14.0, 4.4 Hz, 1H), 1.56 to 1.43 (m, 1H), 1.37 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 144.7, 133.2, 128.7, 128.0, 127.5, 127.3, 127.1, 126.4, 118.9,

118.7, 72.6, 69.2, 67.1, 59.3, 58.2, 44.4, 44.1, 40.0, 29.8, 29.1, 28.9, 28.5, 28.4, 18.3. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{22}H_{32}N_2O_2$ 356.2464; found 356.5017.



13d

Prepped from aryl ketopiperazine (334.2 mg, 1 mmol, 1.0 equiv. made via General Procedure A-C) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Yield = 328.5 mg, 85%. ^{1}H NMR (400 MHz, CDCl3) δ 7.24 (s, 1H), 6.91 to 6.78 (m, 3H), 6.08 (dt, *J* = 16.7, 9.0 Hz, 1H), 5.34 to 5.22 (m, 2H), 4.71 (s, 1H), 3.79 (s, 4H), 3.12 (d, *J* = 4.2 Hz, 1H), 2.68 (s, 1H), 2.49 (dt, *J* = 15.6, 7.6 Hz, 1H), 2.43 (s, 3H), 2.37 to 2.27 (m, 1H), 1.65 (dd, *J* = 14.2, 4.4 Hz, 1H), 1.55 to 1.42 (m, 2H), 1.38 (s, 9H), 1.34 to 1.21 (m, 3H), 0.98 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 158.6, 136.5, 134.3, 133.8, 133.2, 127.5, 118.9, 118.6, 114.0, 113.3, 72.5, 71.8, 69.3, 67.1, 59.2, 58.7, 58.4, 57.7, 56.3, 55.3, 40.0, 29.8, 29.4, 29.2, 28.8, 28.4, 18.2. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{23}H_{34}N_2O_3$ 386.2569; found 386.5277.



13e

Prepped from aryl ketopiperazine (338.2 mg, 1 mmol, 1.0 equiv. made via General Procedure A-C) and allyl magnesium bromide solution (2.0 mL, 1.0 M in diethyl ether, 3 equiv), using General Procedure E. Yield = 277.3 mg, 71%. ^{1}H NMR (400 MHz, CDCl3) δ 7.37 (q, *J* = 7.0, 6.3 Hz, 2H), 7.35 to 7.24 (m, 4H), 7.16 (dd, *J* = 6.5, 3.0 Hz, 2H), 5.86 (dd, *J* = 14.0, 6.5 Hz, 2H), 5.12 (d, *J* = 10.4 Hz, 1H), 5.00 (dd, *J* = 30.0, 13.4 Hz, 1H), 3.78 (s, 1H), 3.41 (d, *J* = 13.8 Hz, 1H), 3.21 (d, *J* = 4.7 Hz, 1H), 2.81 (s, 1H), 2.50 (s, 3H), 2.27 (dt, *J* = 12.5, 6.0 Hz, 1H), 2.05 (s, 3H), 1.97 (dd, *J* = 14.4, 7.5 Hz, 1H), 1.41 (dd, *J* = 14.1, 4.2 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 141.1, 136.9, 133.0, 129.7, 128.8, 128.6, 128.5, 128.2, 128.1, 127.4, 118.5, 72.0, 68.6, 65.0, 57.2, 47.1, 44.5, 42.9, 38.4, 29.8, 18.1. **HRMS-EI$^+$** (*m/z*): calc'd for $C_{25}H_{30}N_2O_2$ 390.2307; found 390.5179.

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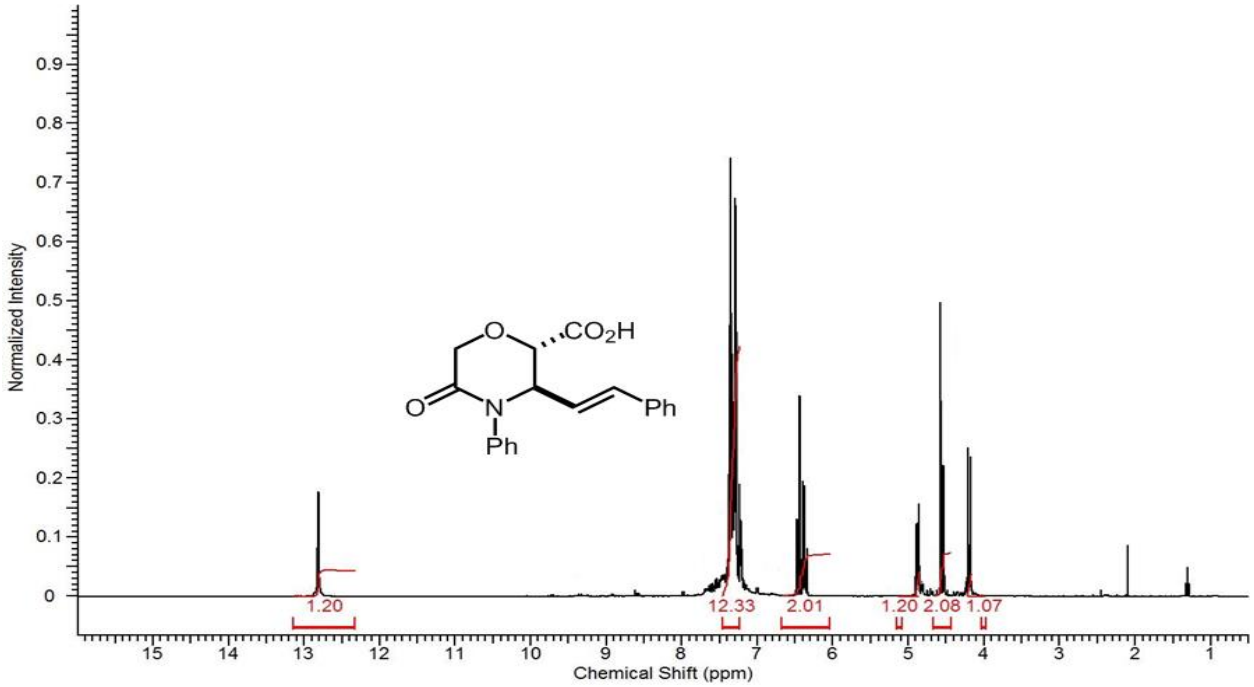
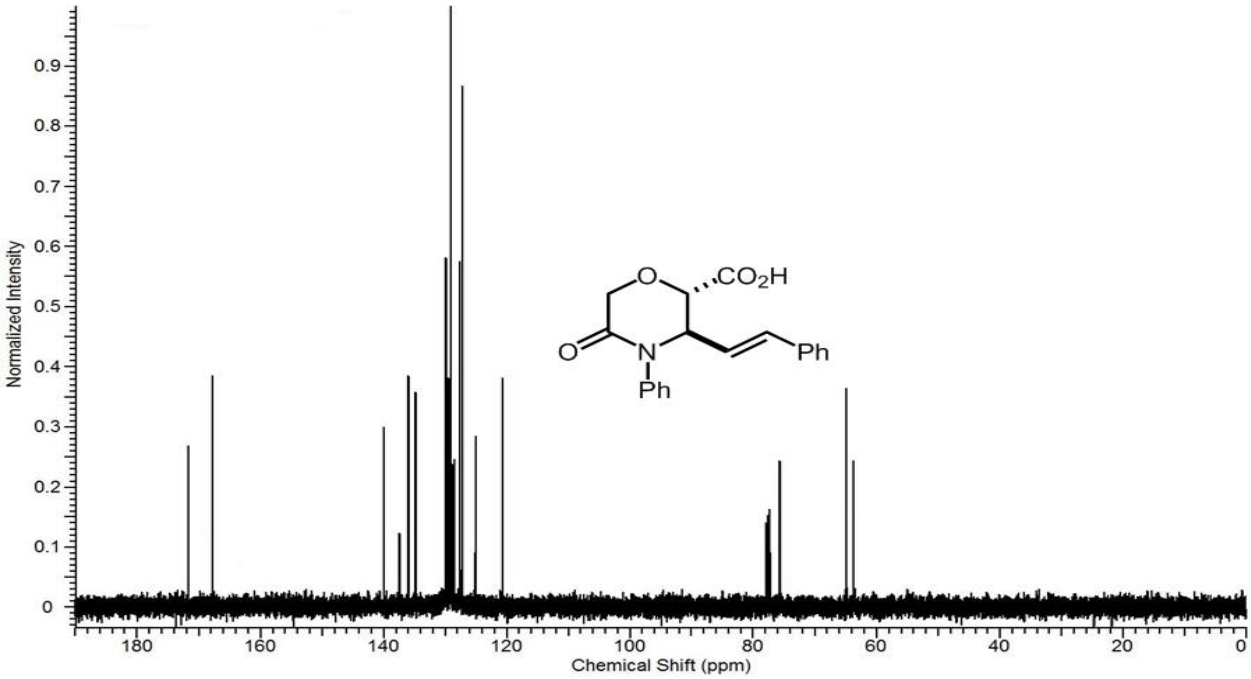
APPENDIXES

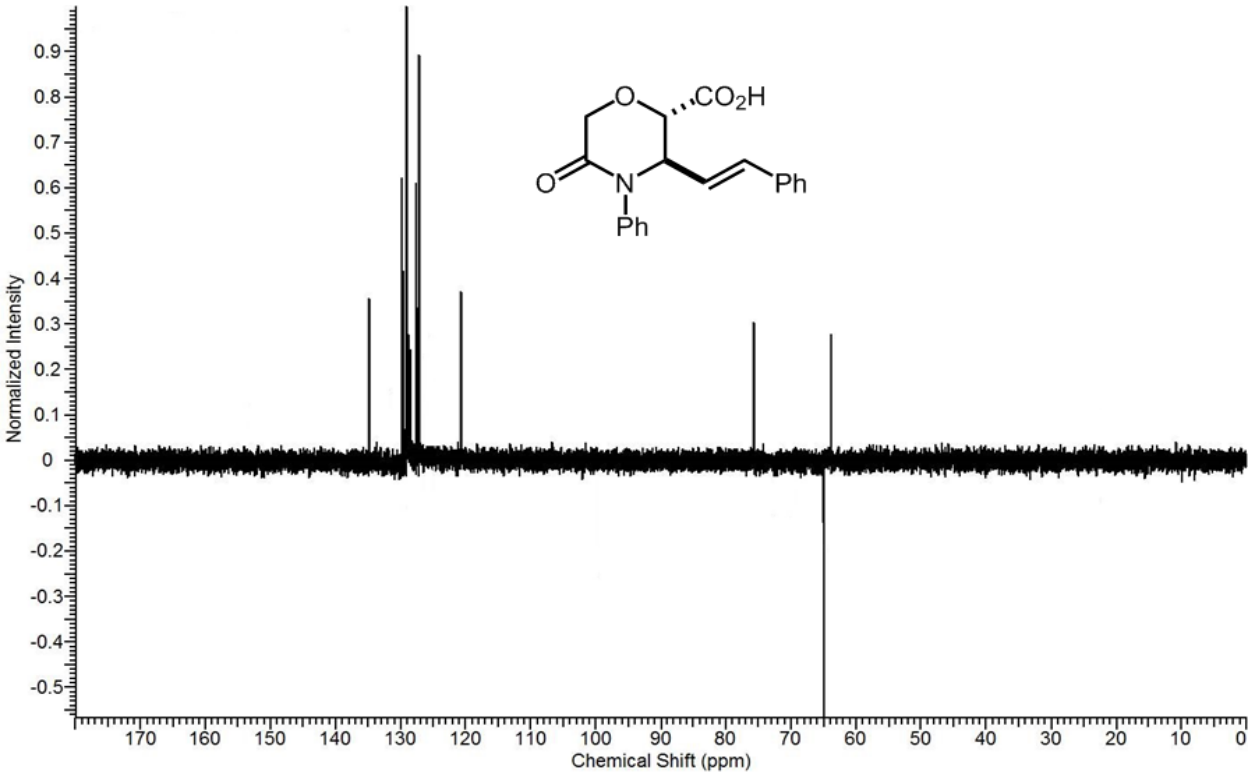
Appendix A: Spectral Data for Chapter 2



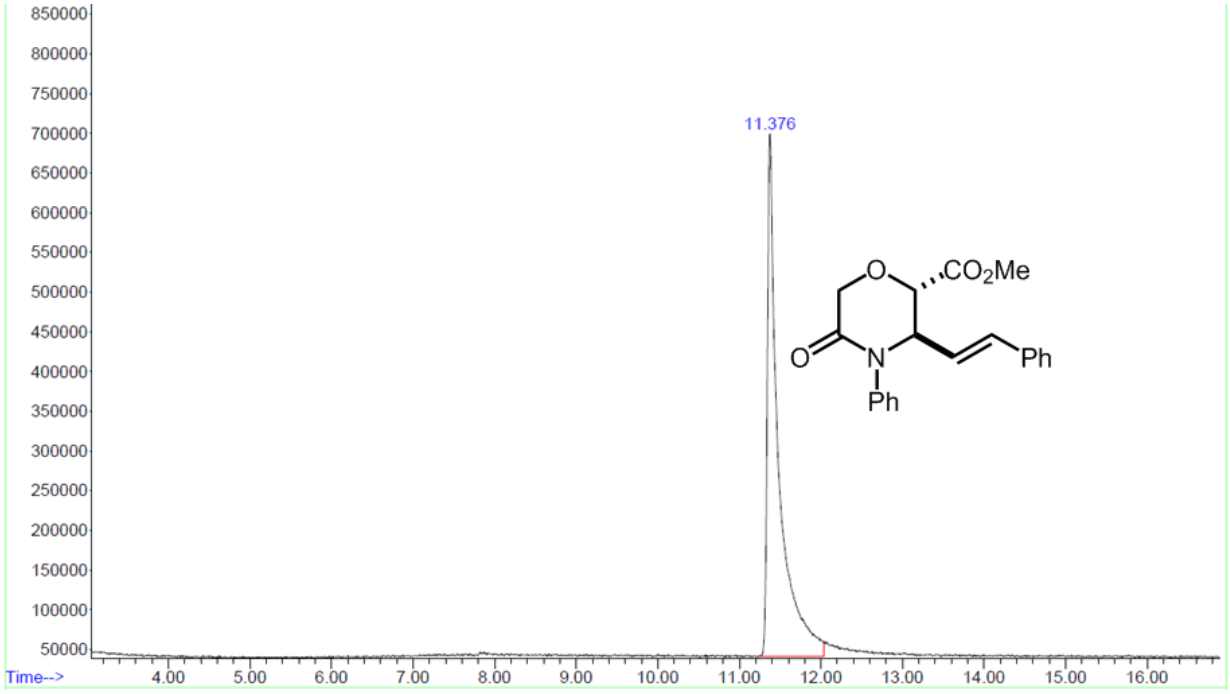
Spectrum 1-1: ^{1}H NMR spectrum of **5a1.**



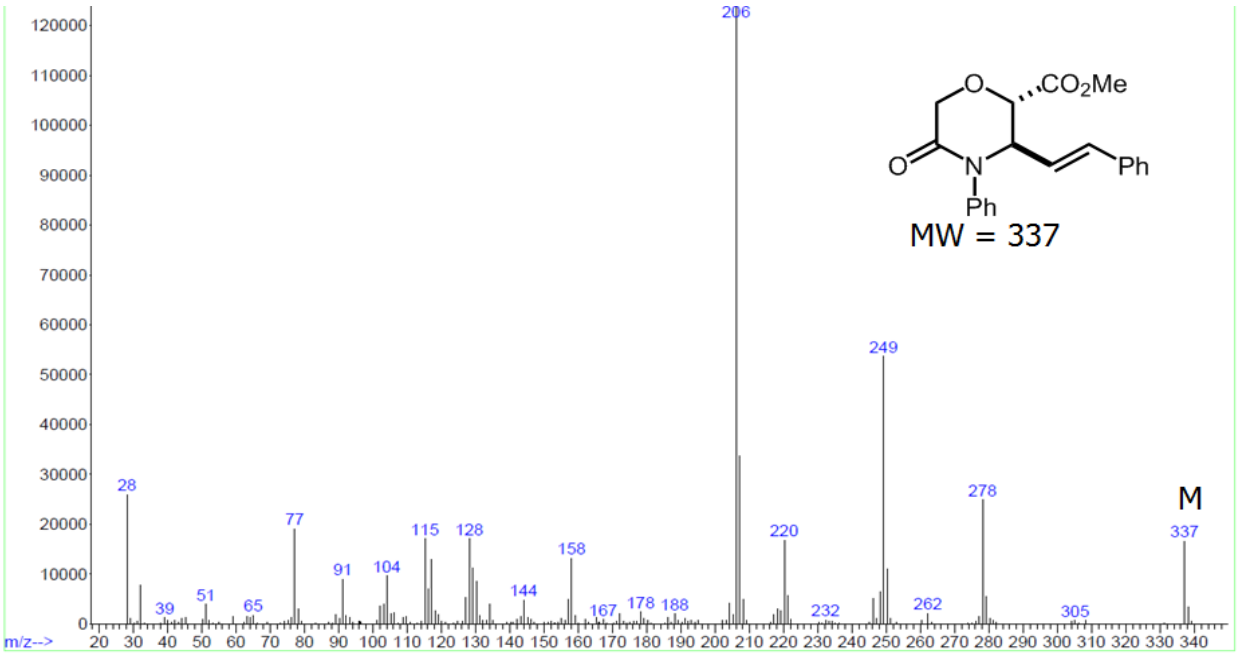
Spectrum 1-2: ^{13}C NMR spectrum of **5a1.**



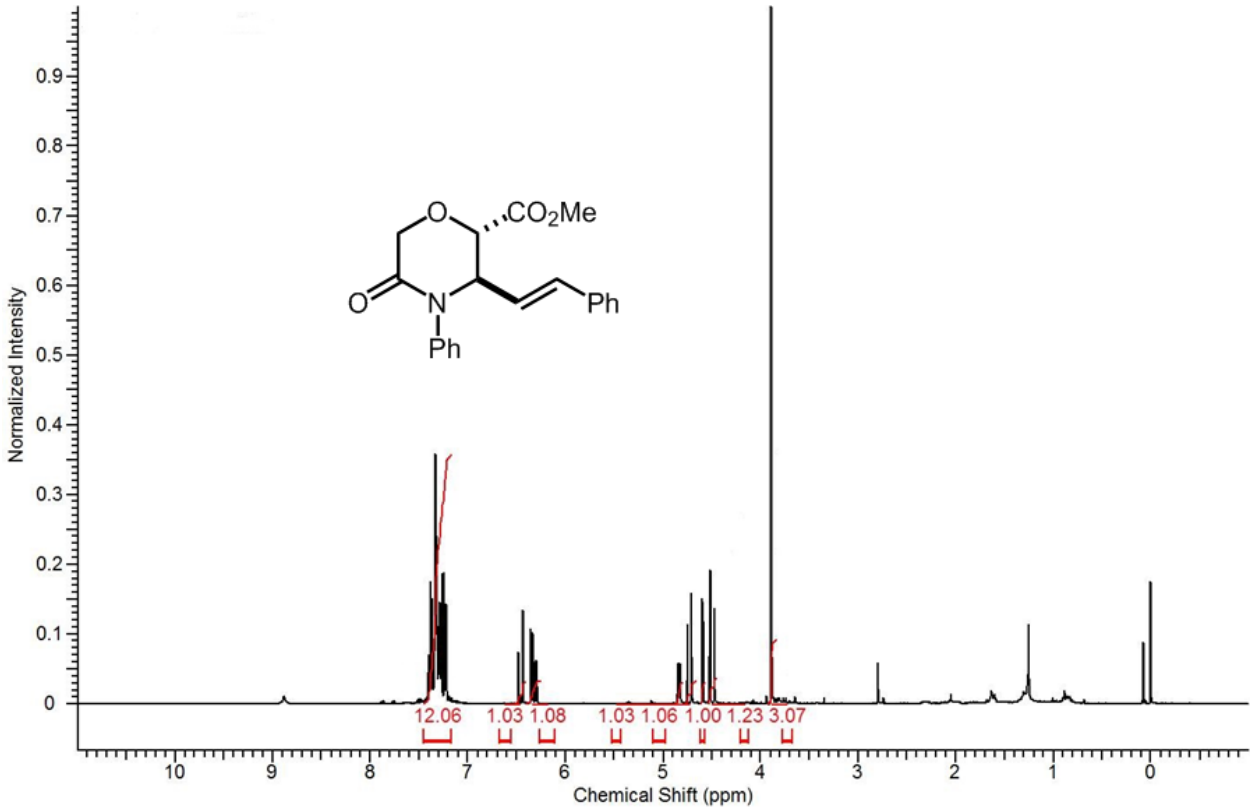
Spectrum 1-3: DEPT-135 NMR spectrum of **5a1.**



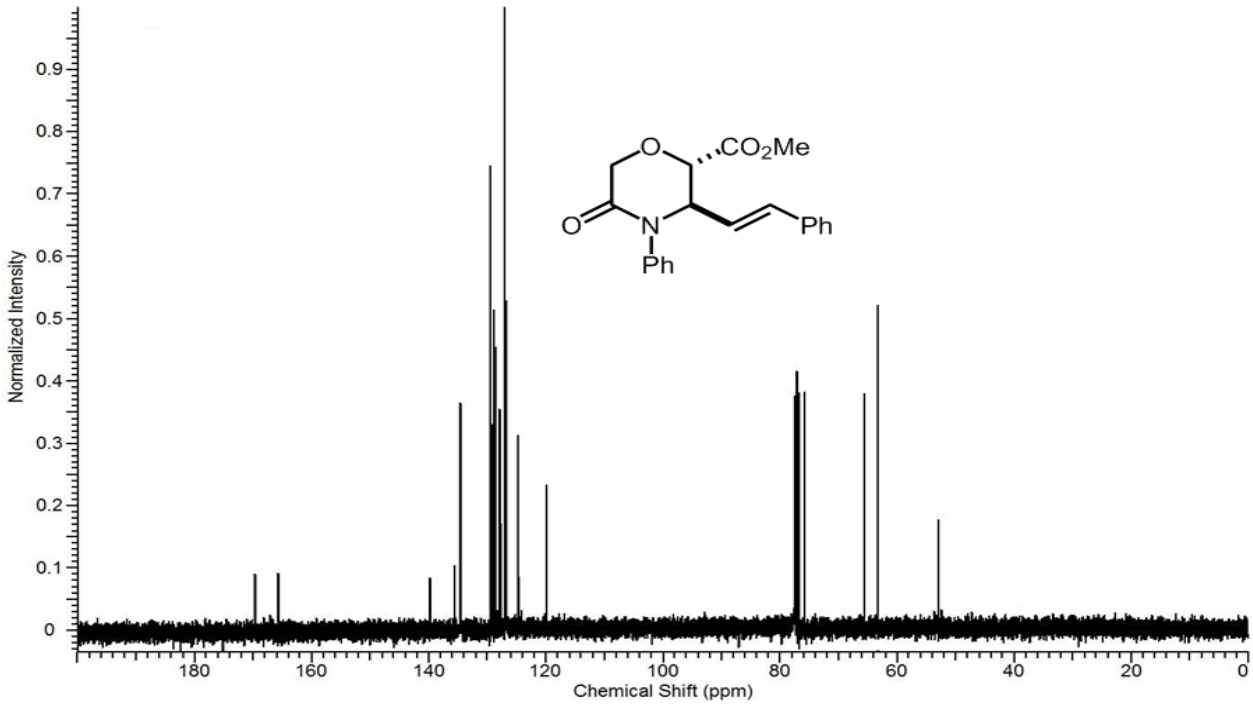
Spectrum 1-4: GC spectrum of **5a2.**



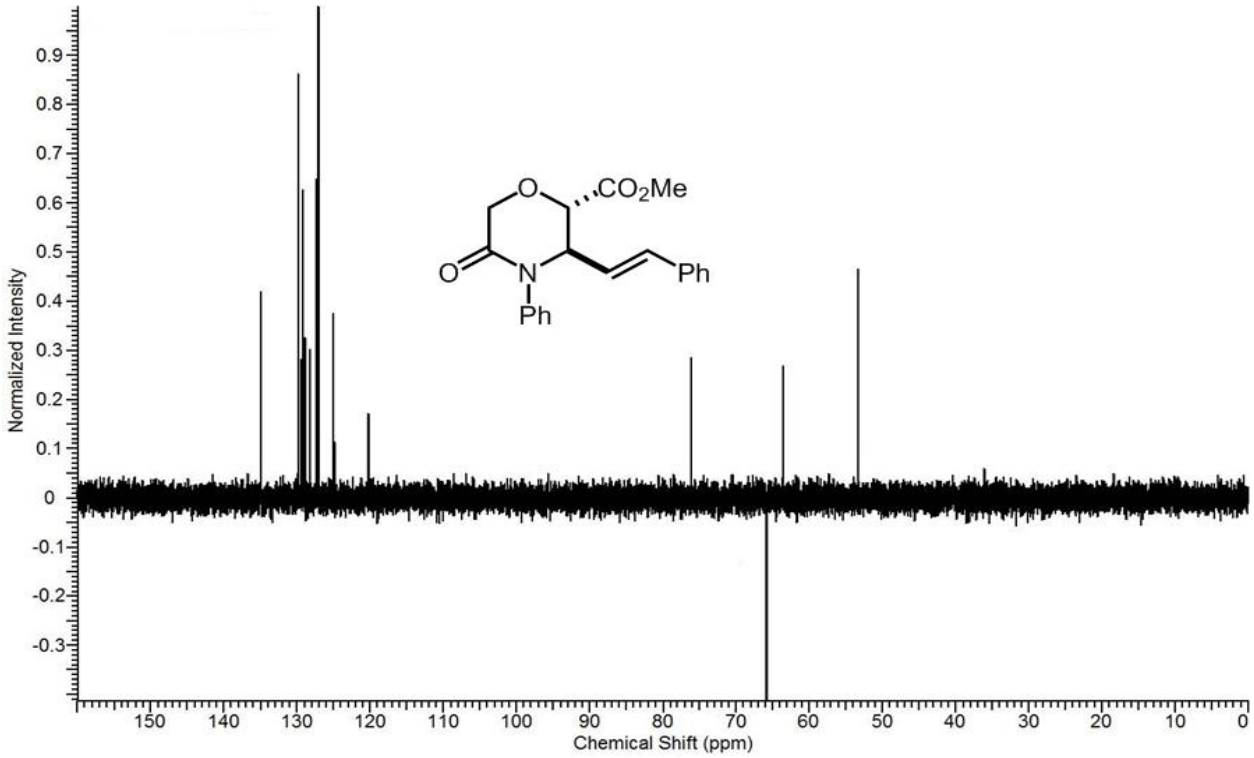
Spectrum 1-5: MS spectrum of **5a2.**



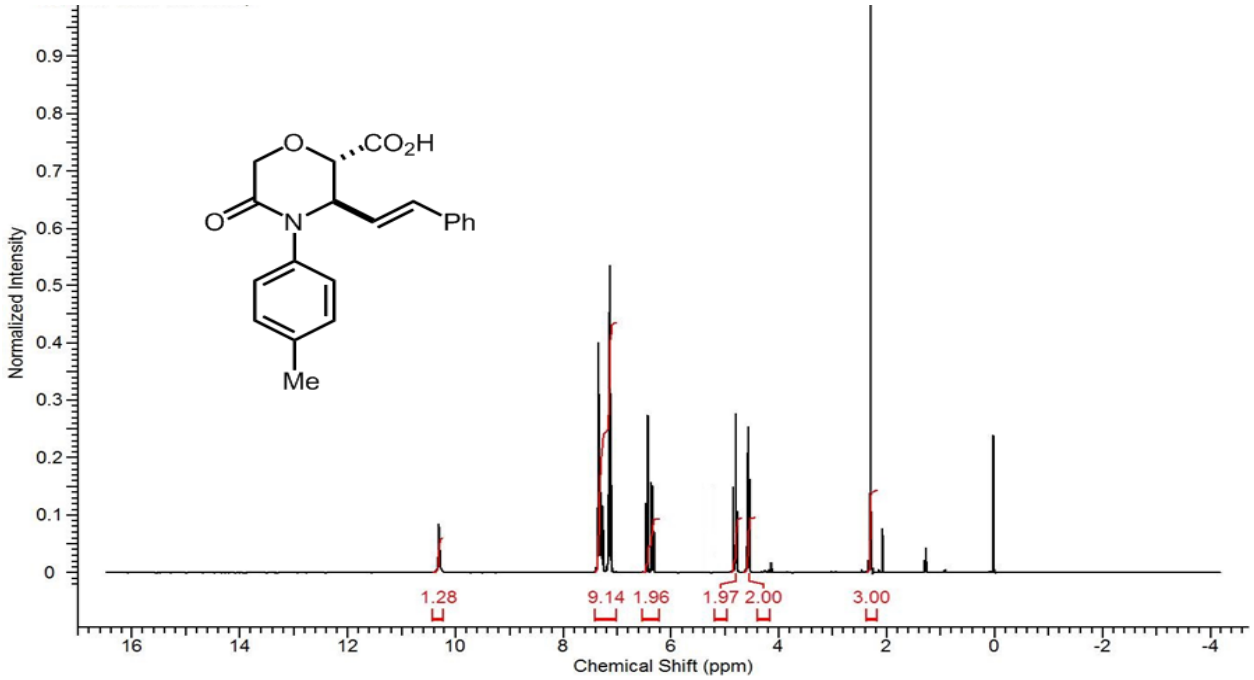
Spectrum 1-6: ^{1}H spectrum of **5a2.**



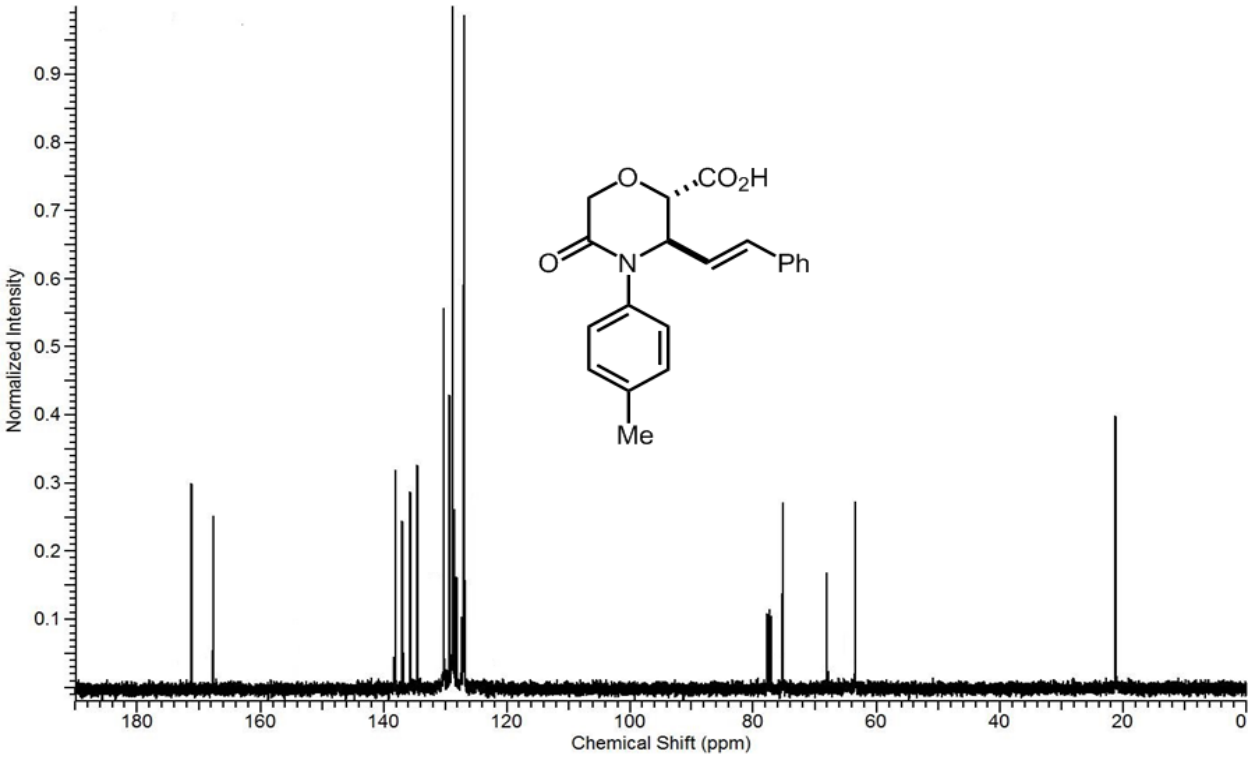
Spectrum 1-7: ^{13}C NMR spectrum of **5a2.**



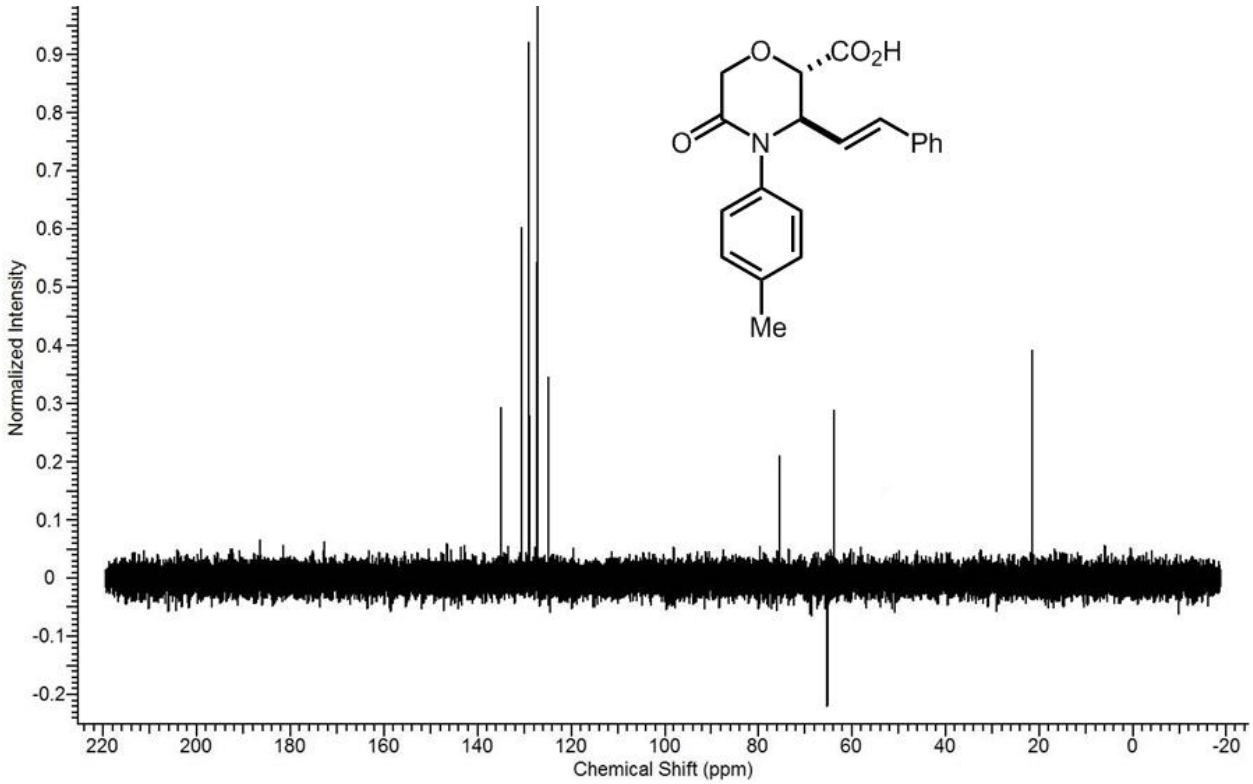
Spectrum 1-8: DEPT-135 NMR spectrum of **5a2.**



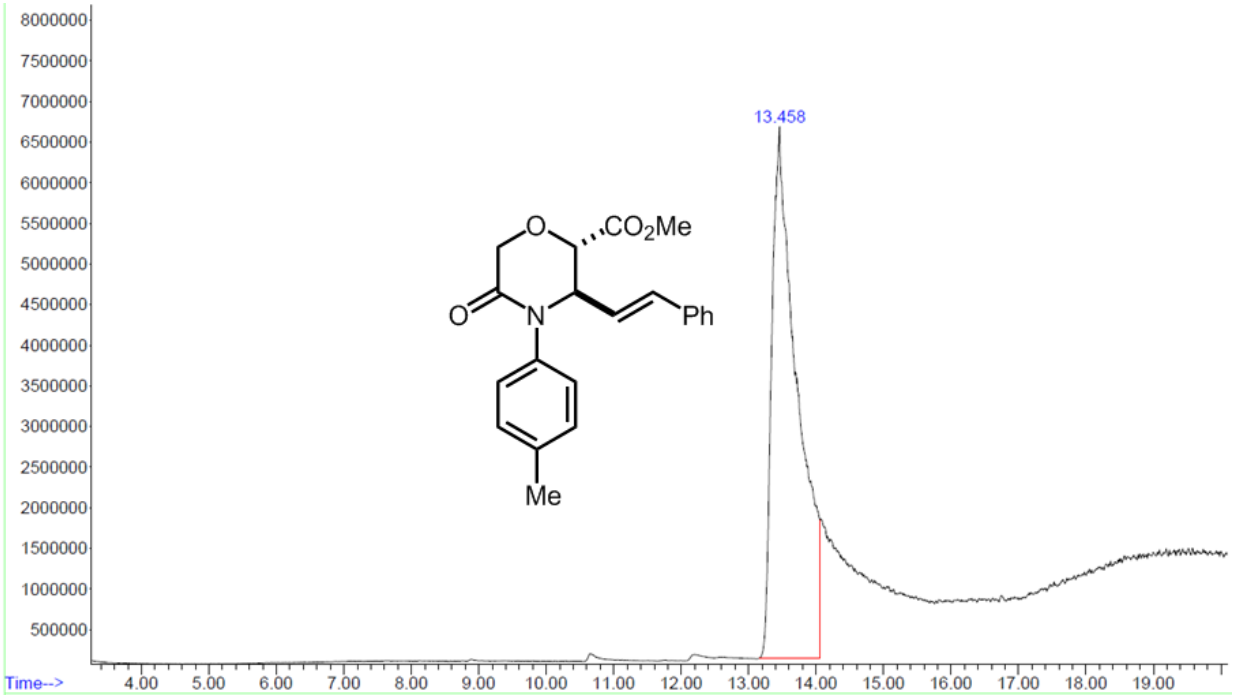
Spectrum 1-9: ^{1}H NMR spectrum of **5b1.**



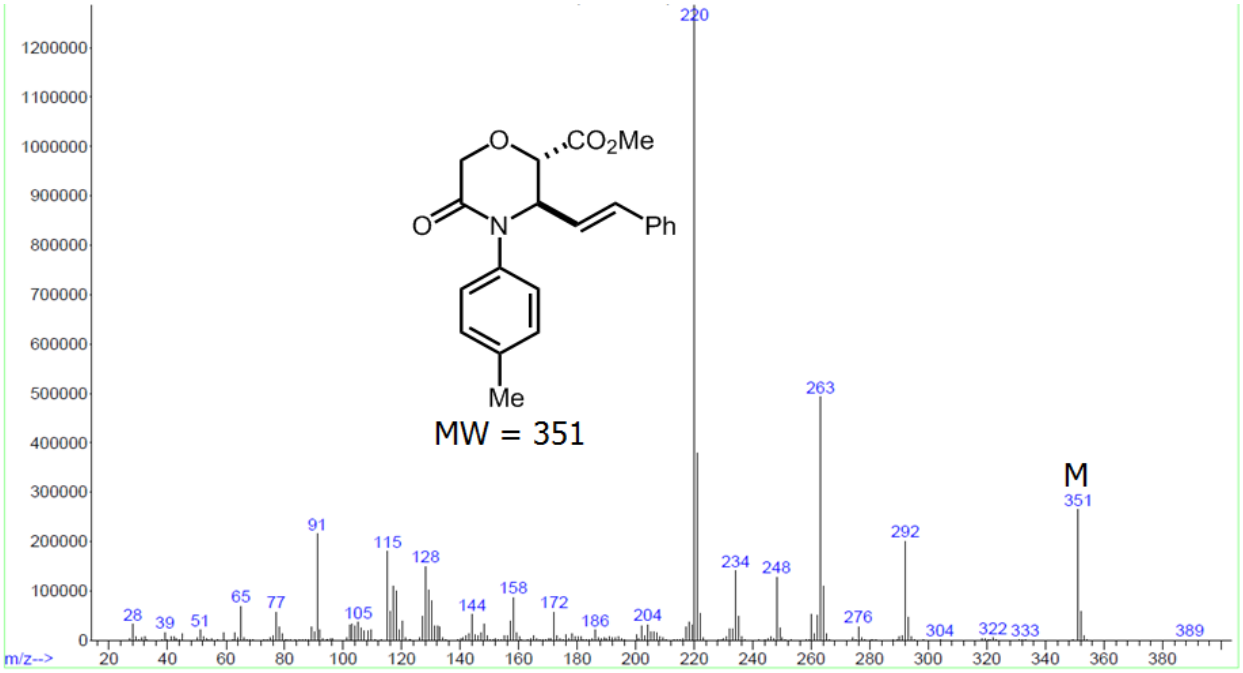
Spectrum 1-10: ^{13}C NMR spectrum of **5b1.**



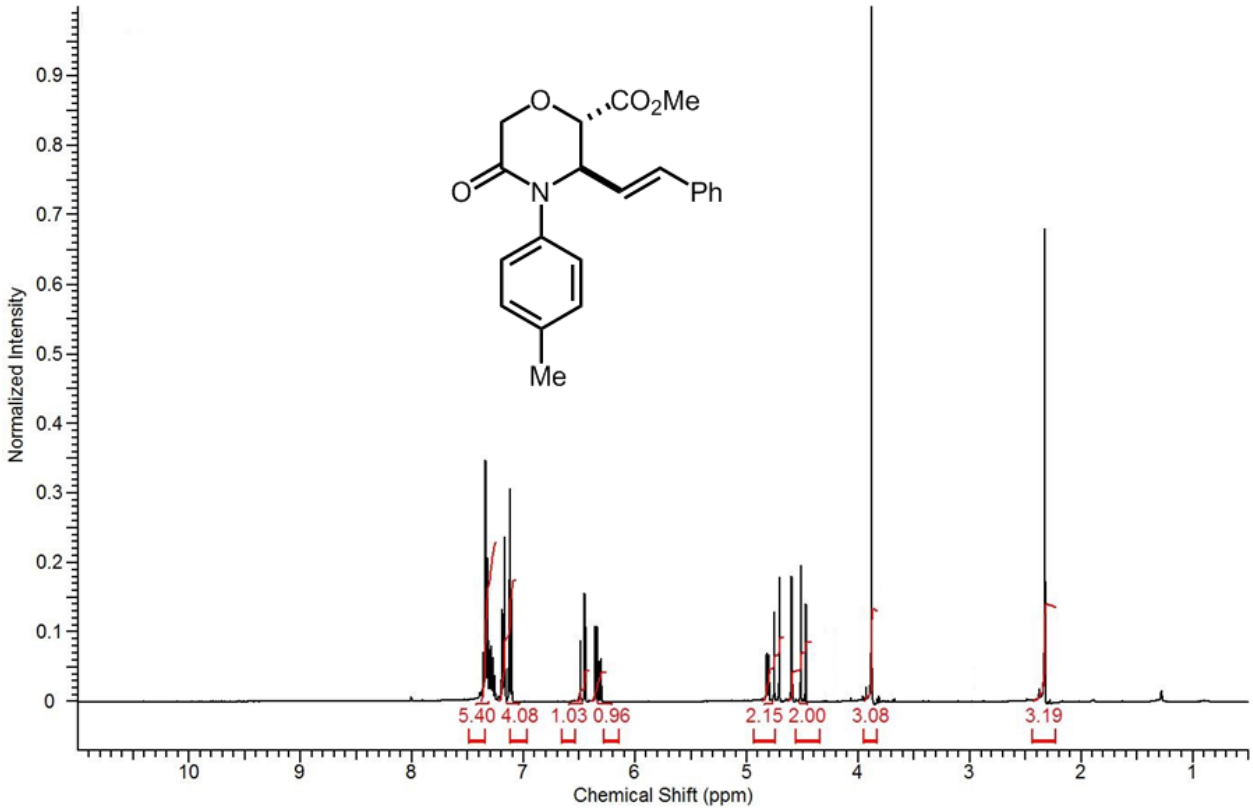
Spectrum 1-11: DEPT-135 NMR spectrum of **5b1.**



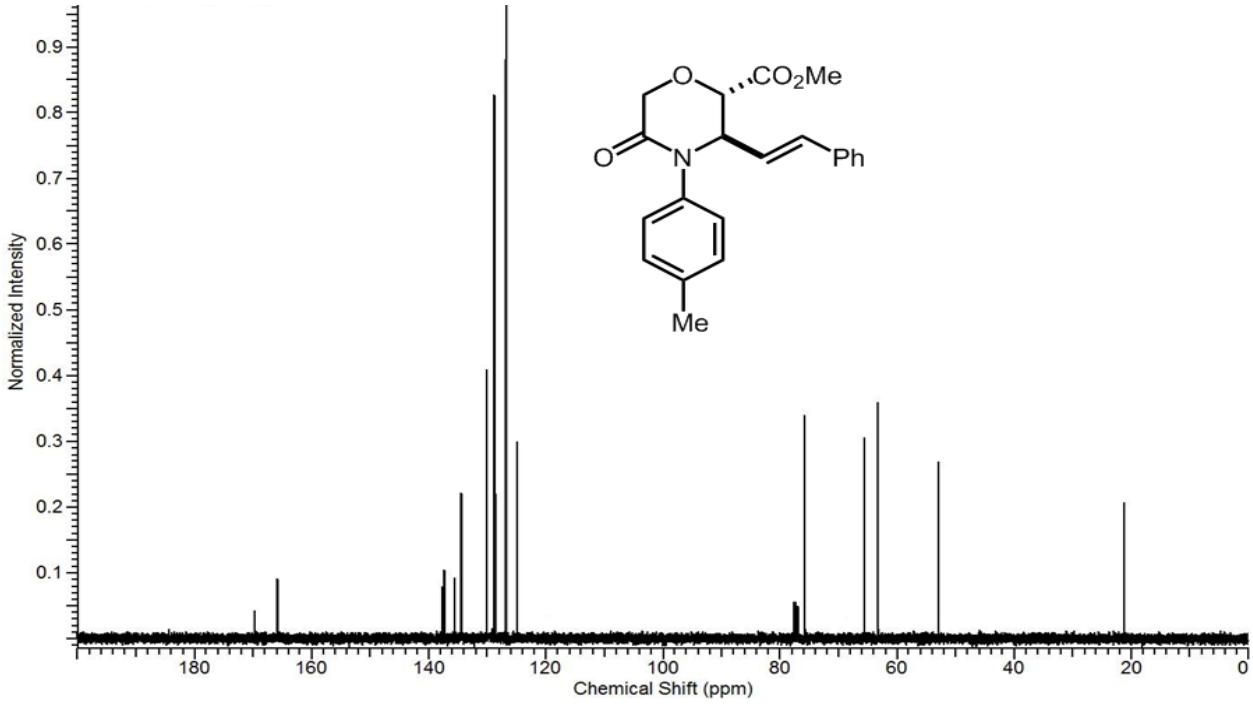
Spectrum 1-12: GC spectrum of **5b2.**



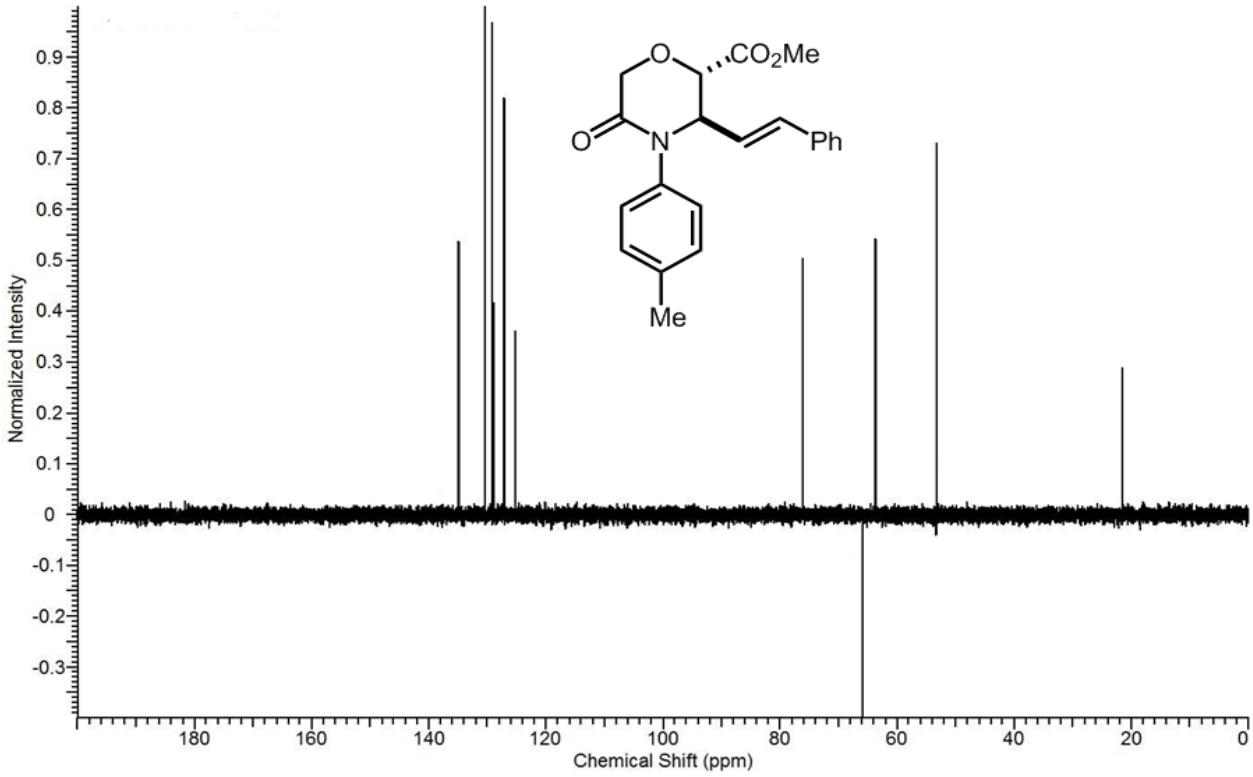
Spectrum 1-13: MS spectrum of **5b2.**



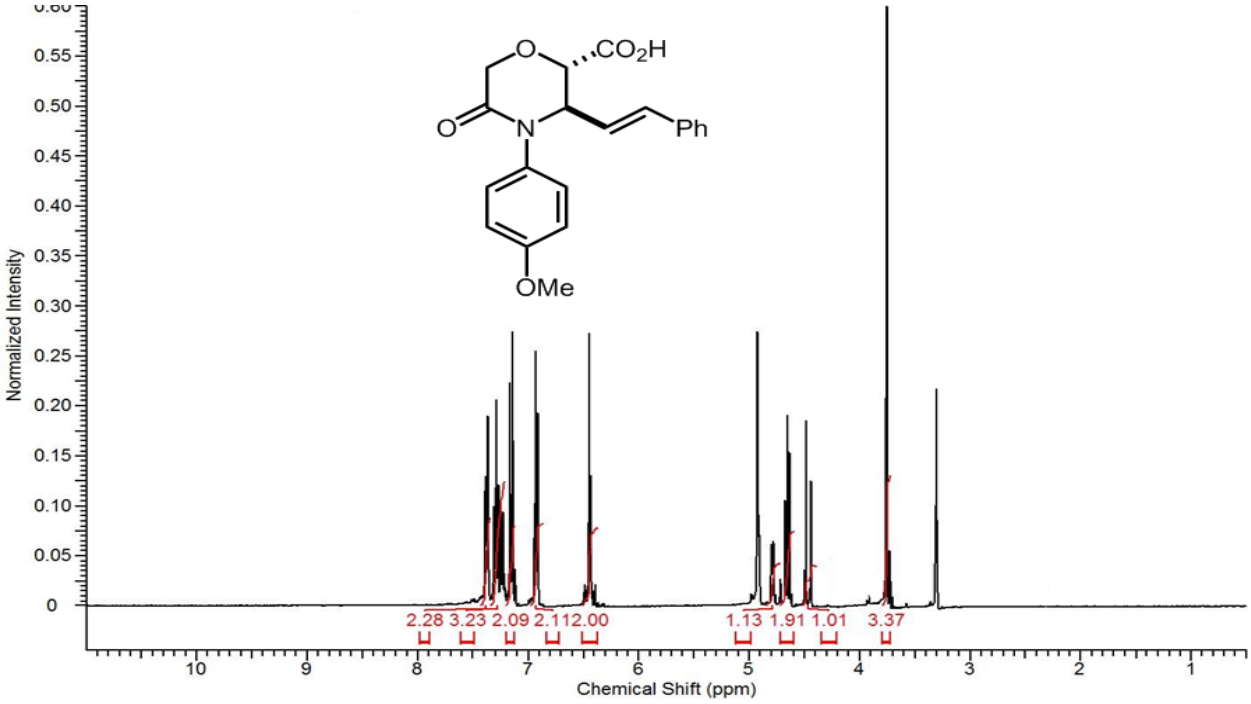
Spectrum 1-14: ^{1}H spectrum of **5b2.**



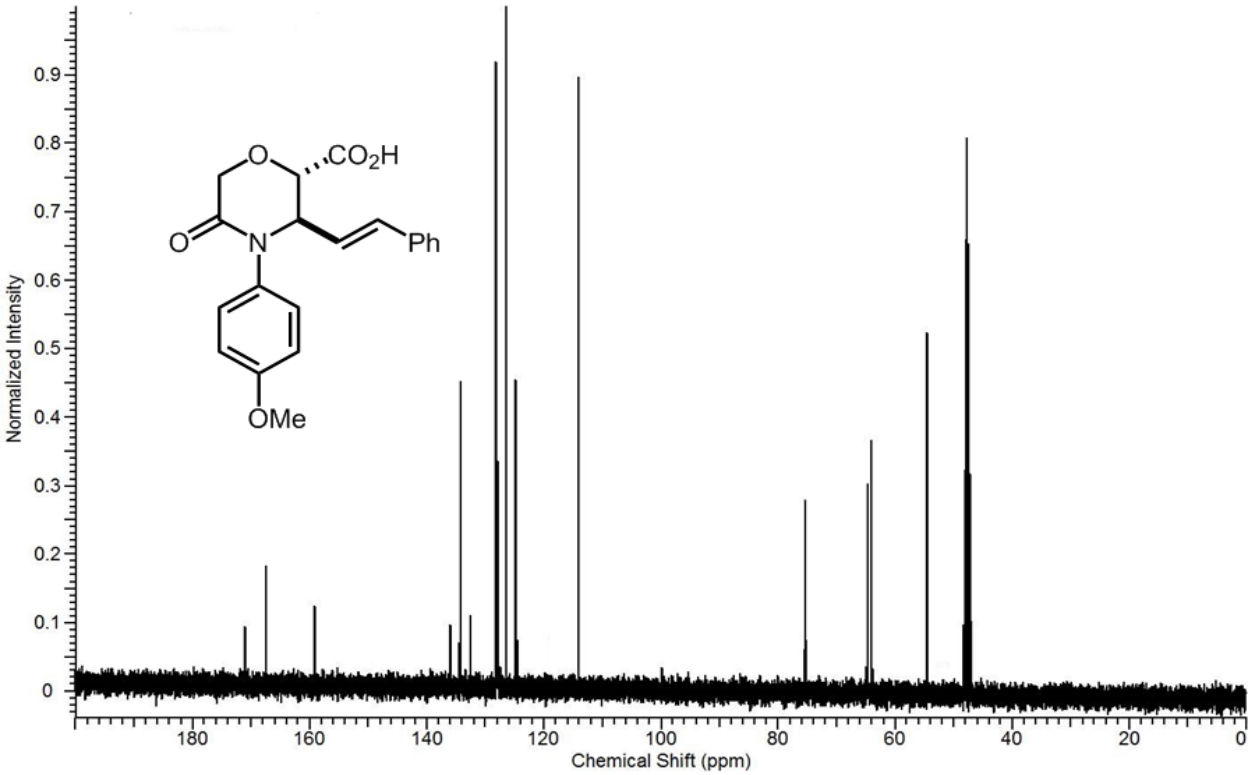
Spectrum 1-15: ^{13}C spectrum of **5b2.**



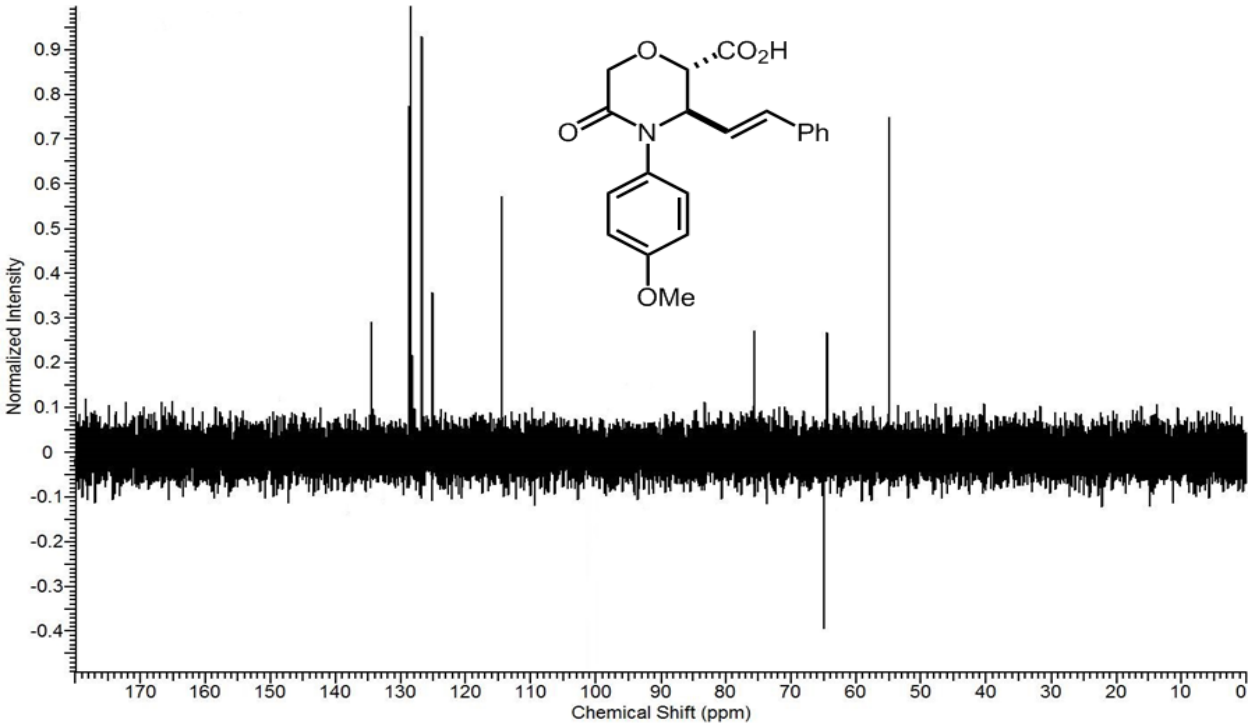
Spectrum 1-16: DEPT-135 spectrum of **5b2.**



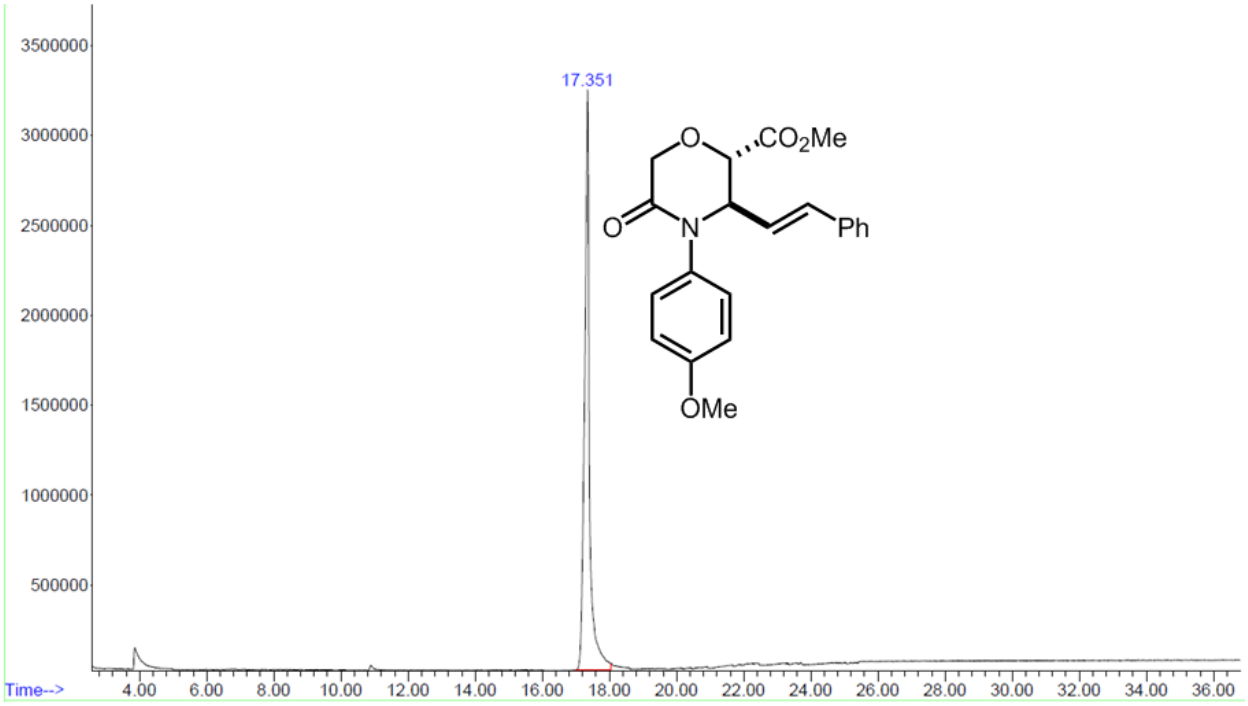
Spectrum 1-17: ^{1}H spectrum of **5c1.**



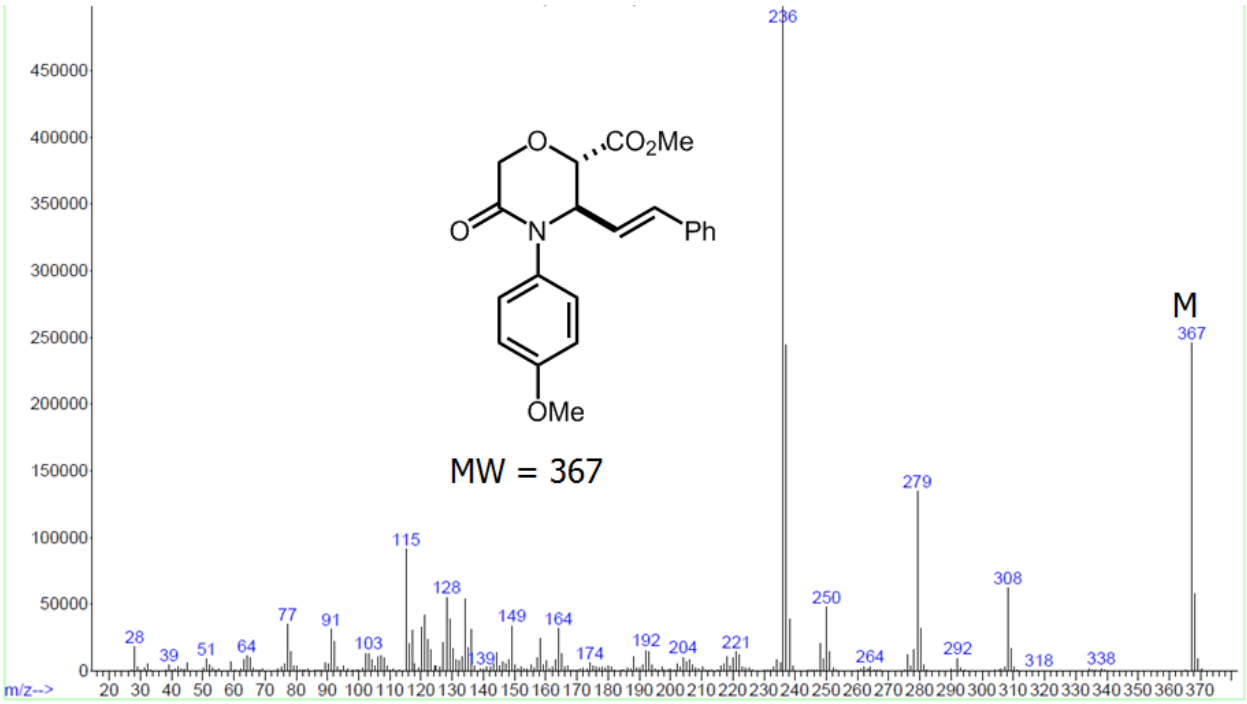
Spectrum 1-18: ^{13}C spectrum of **5c1.**



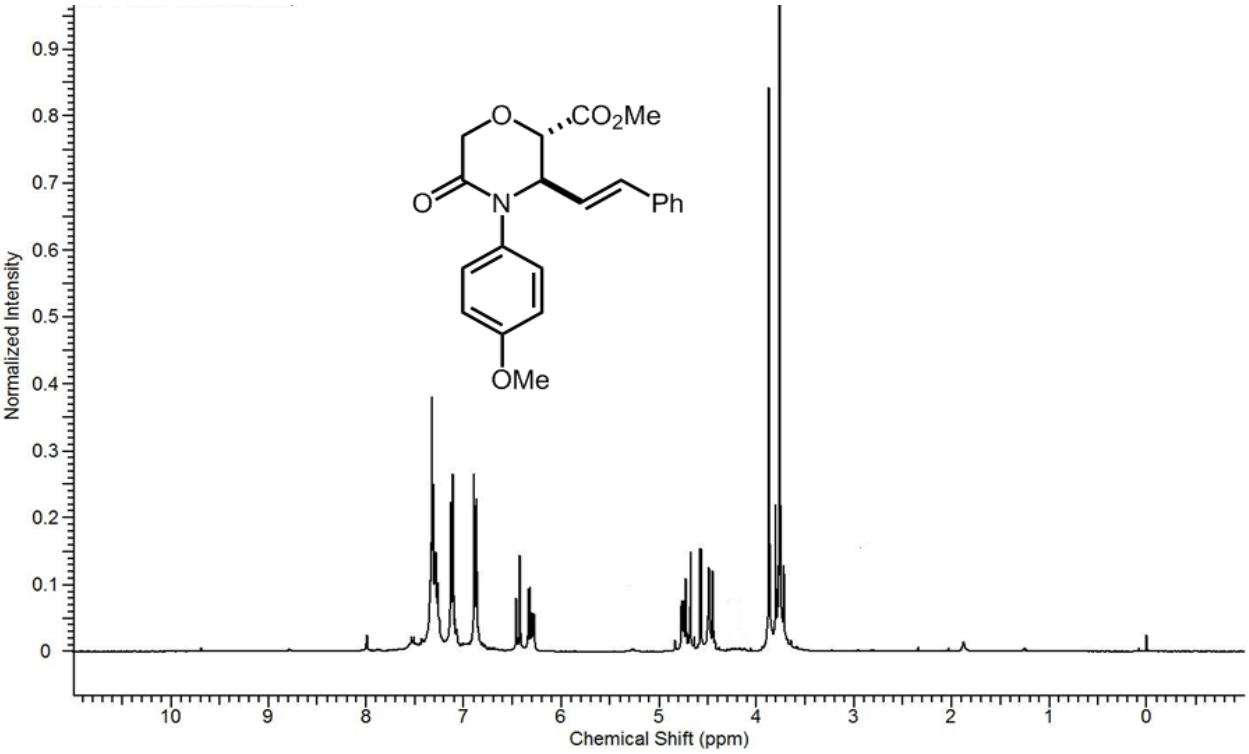
Spectrum 1-19: DEPT-135 spectrum of **5c1.**



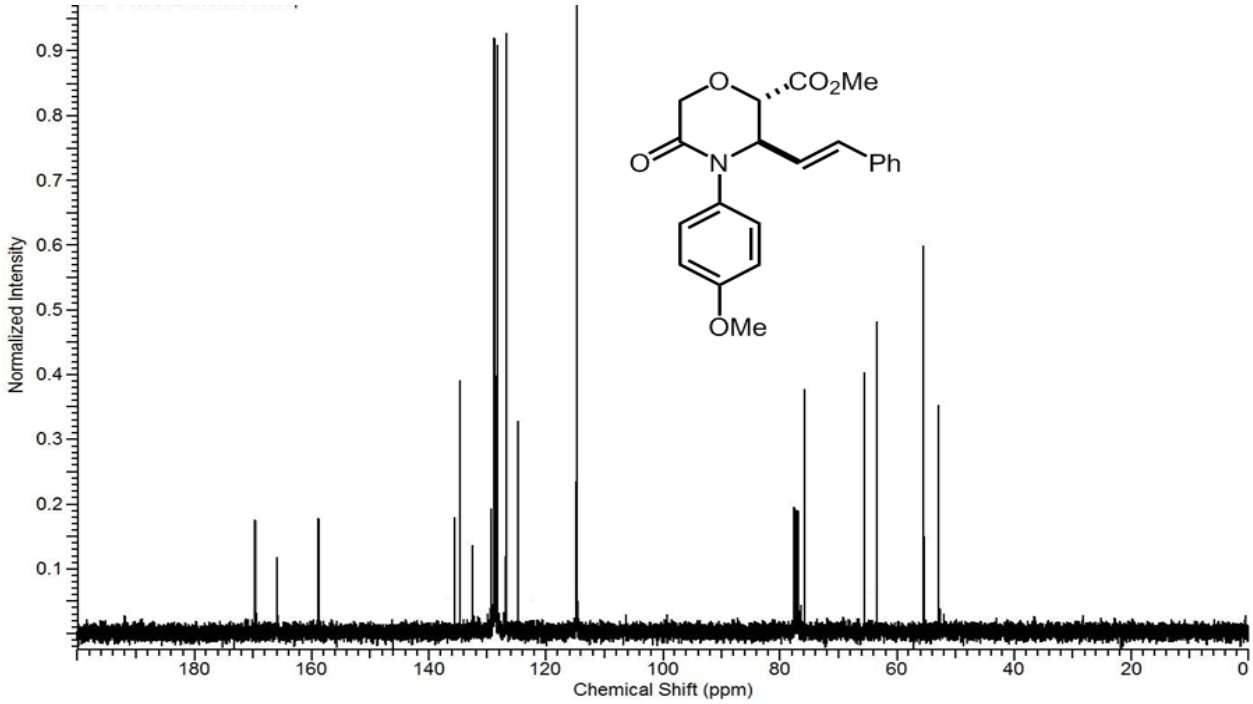
Spectrum 1-20: GC spectrum of **5c2.**



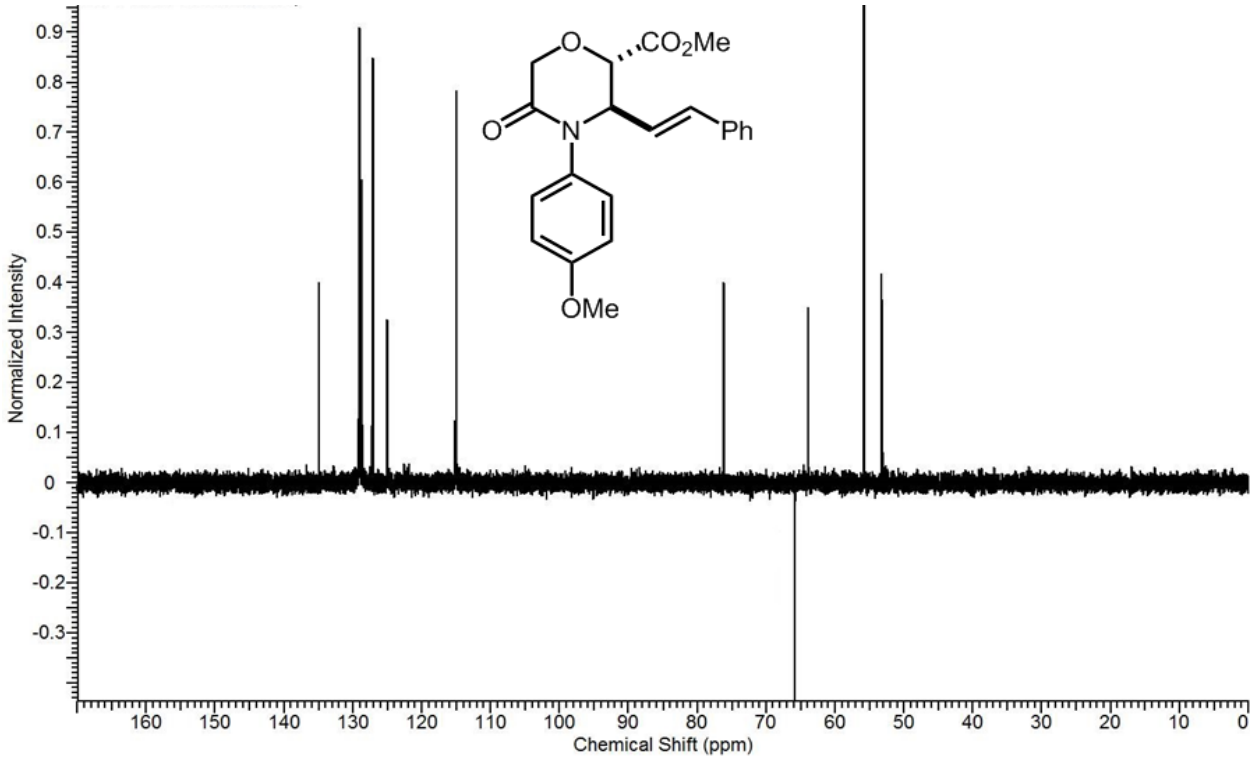
Spectrum 1-21: MS spectrum of **5c2.**



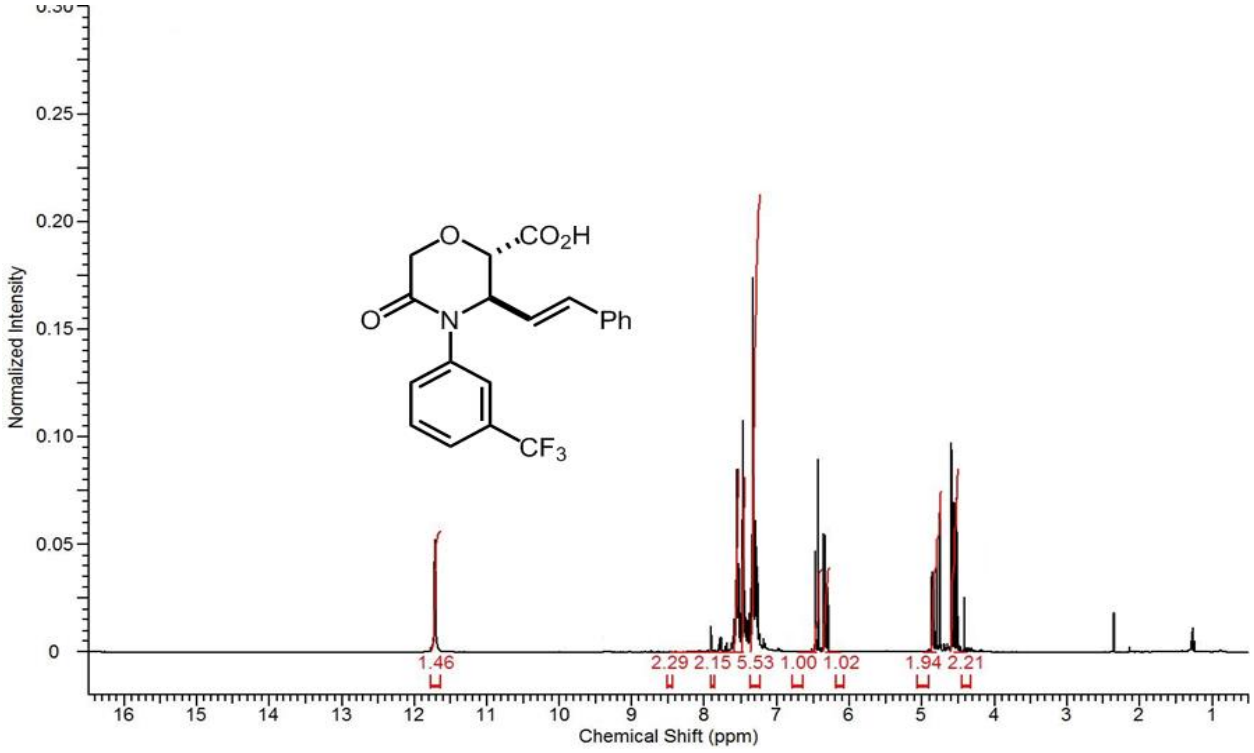
Spectrum 1-22: ^{1}H NMR spectrum of **5c2.**



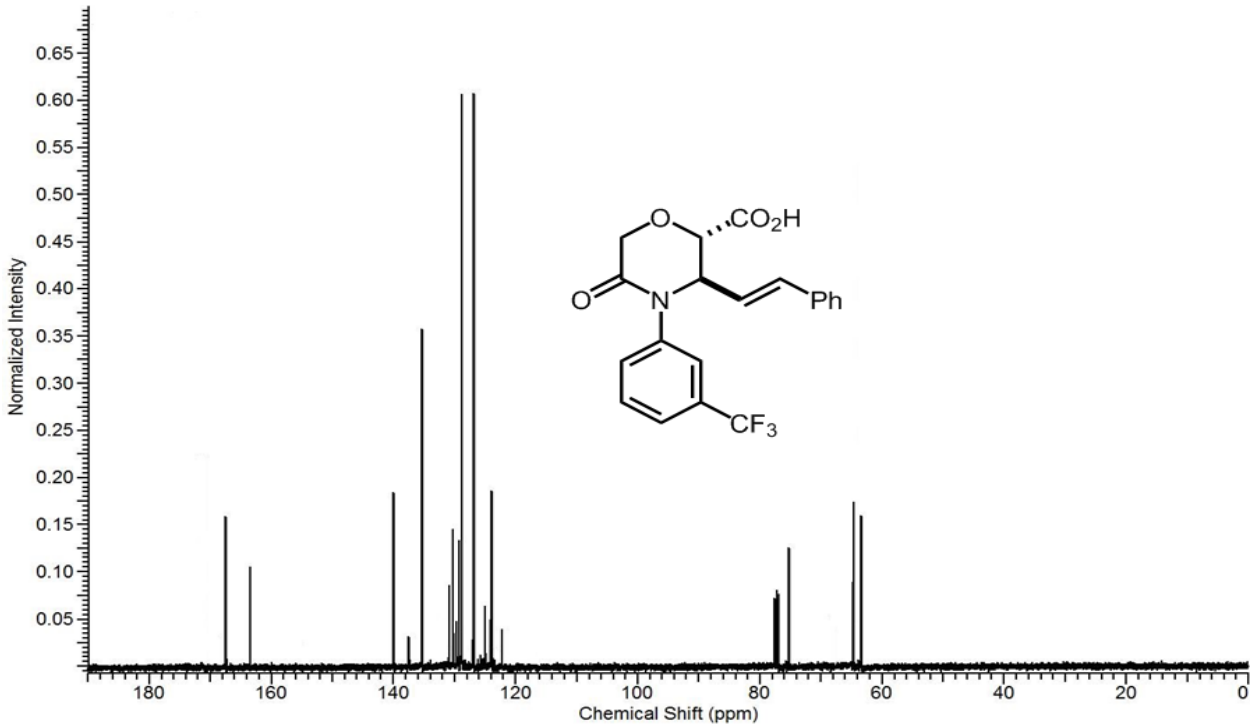
Spectrum 1-23: ^{13}C NMR spectrum of **5c2.**



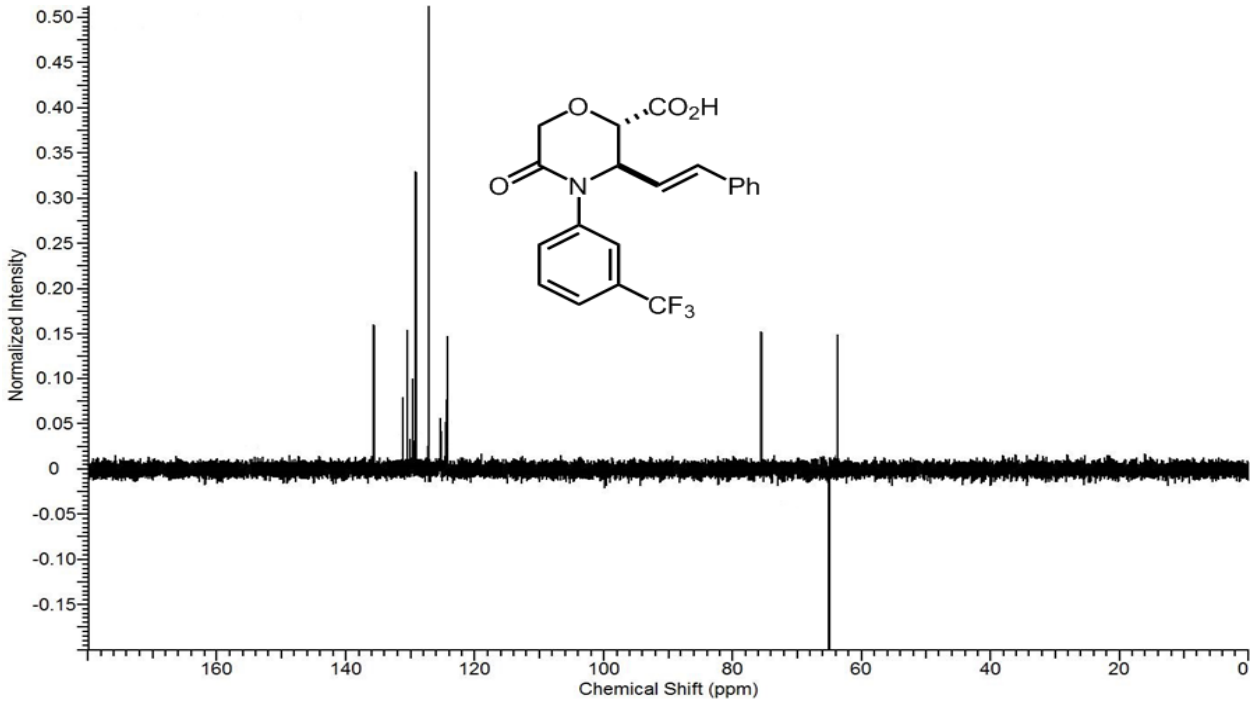
Spectrum 1-24: DEPT-135 NMR spectrum of **5c2.**



Spectrum 1-25: ^{1}H NMR spectrum of **5d1.**



Spectrum 1-25: ^{13}C NMR spectrum of **5d1.**



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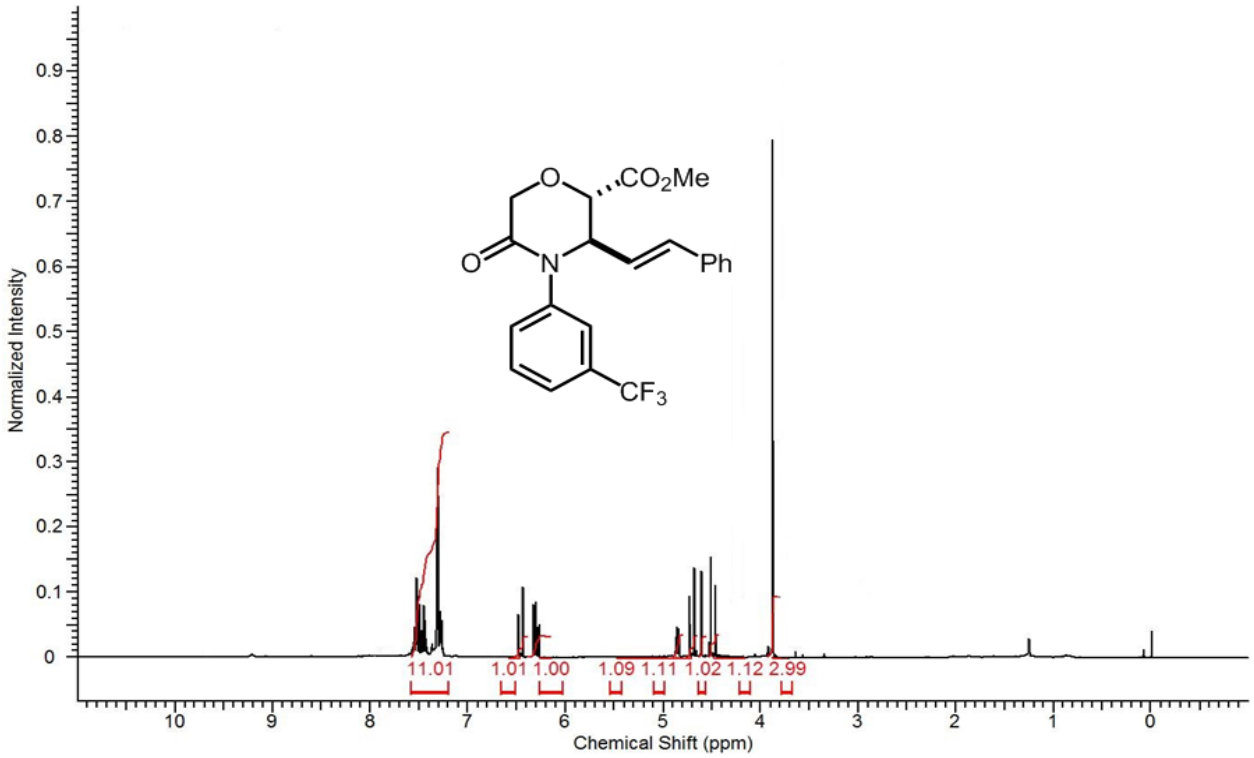
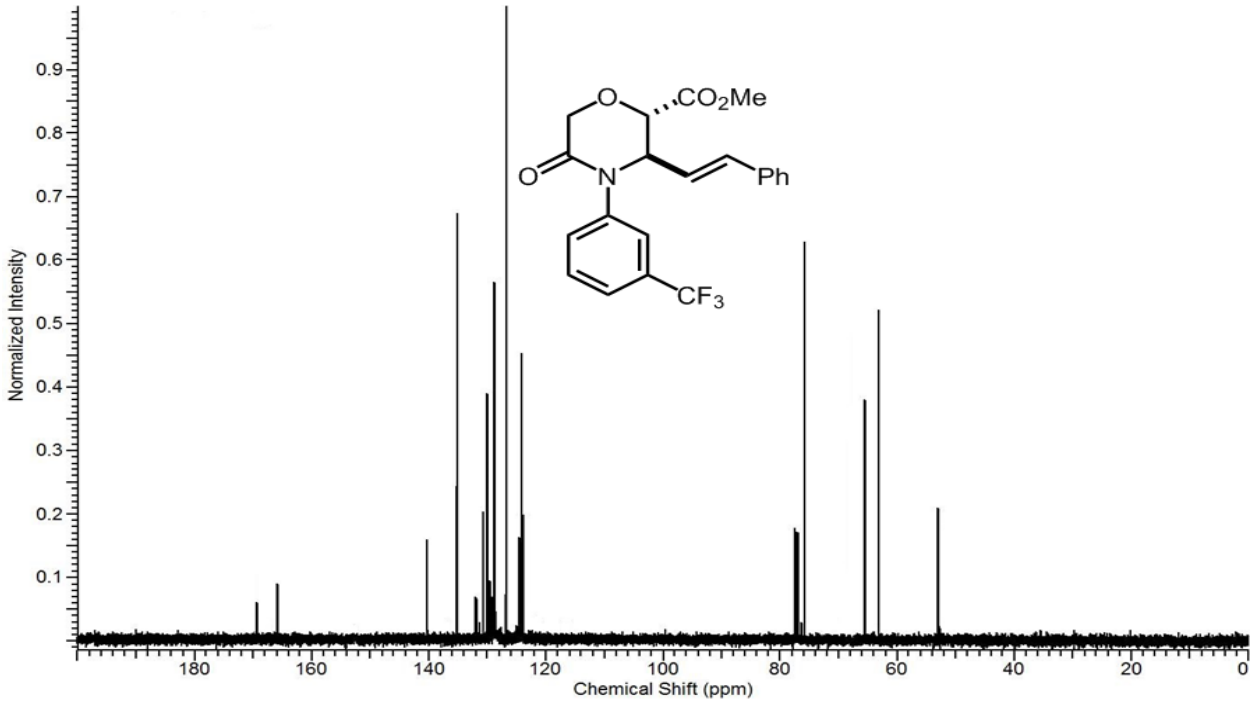
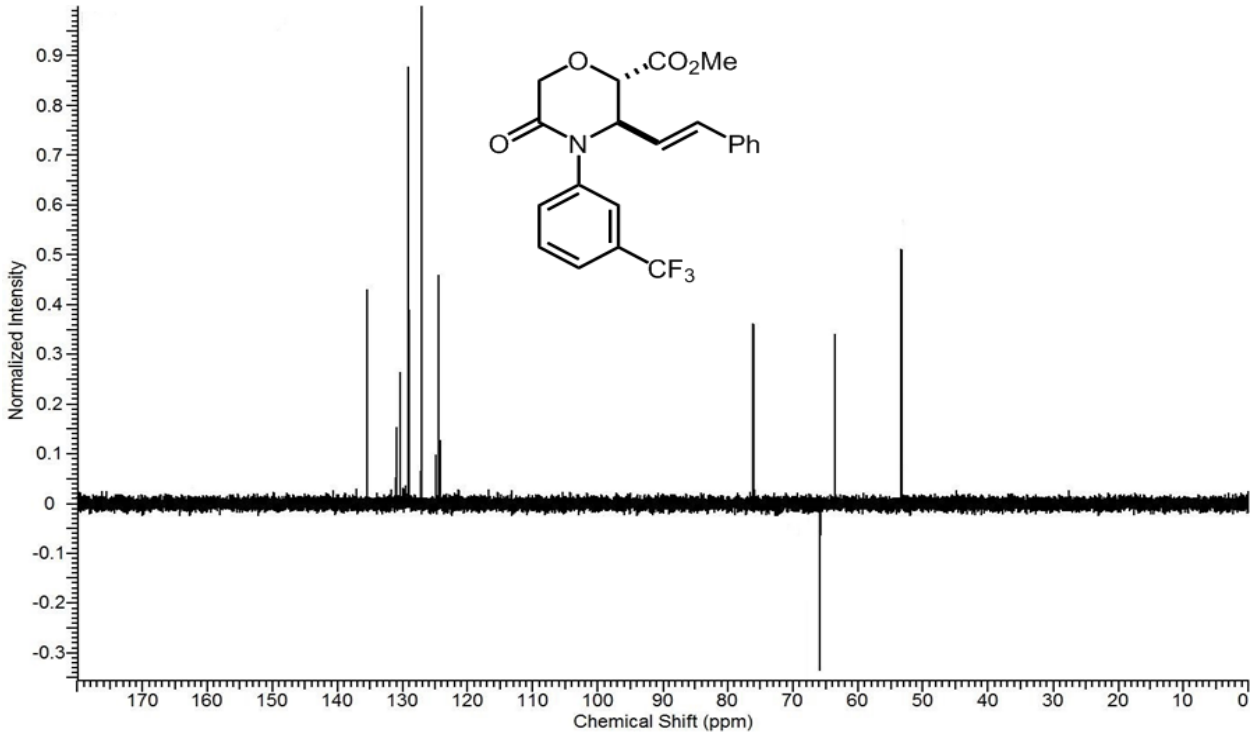


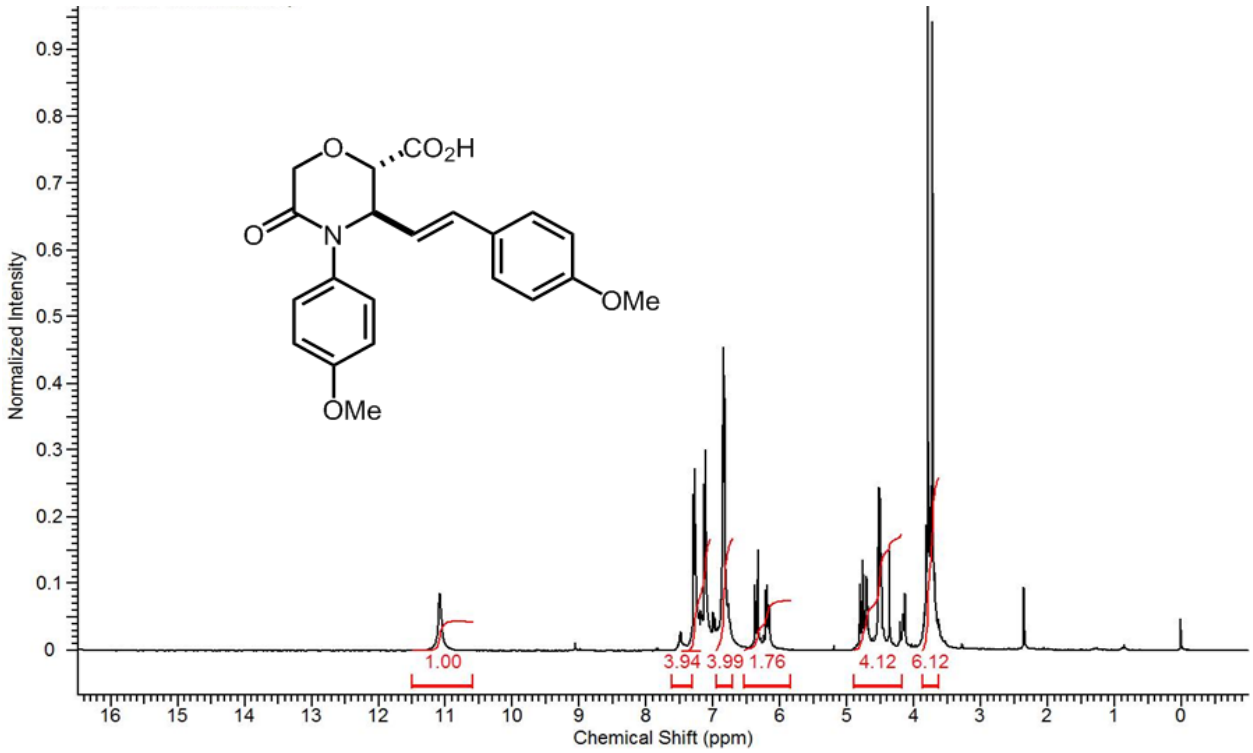
Spectrum 1-27: ^{1}H NMR spectrum of **5d2.**



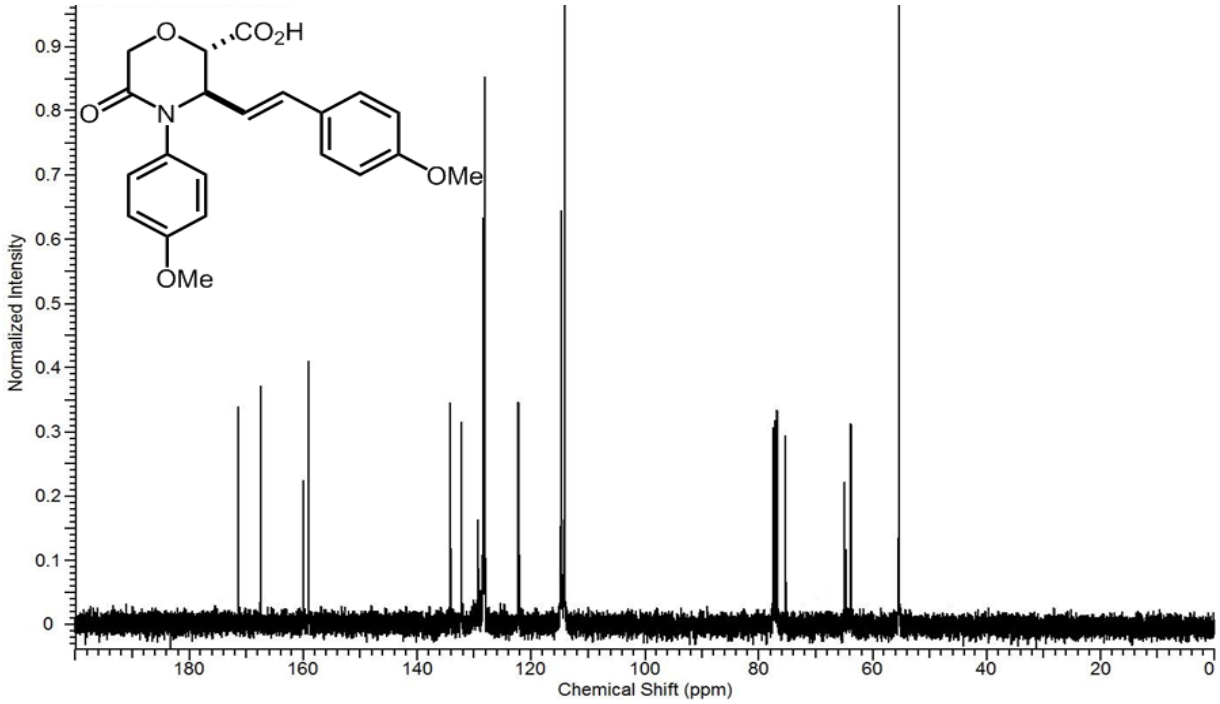
Spectrum 1-28: ^{13}C NMR spectrum of **5d2.**



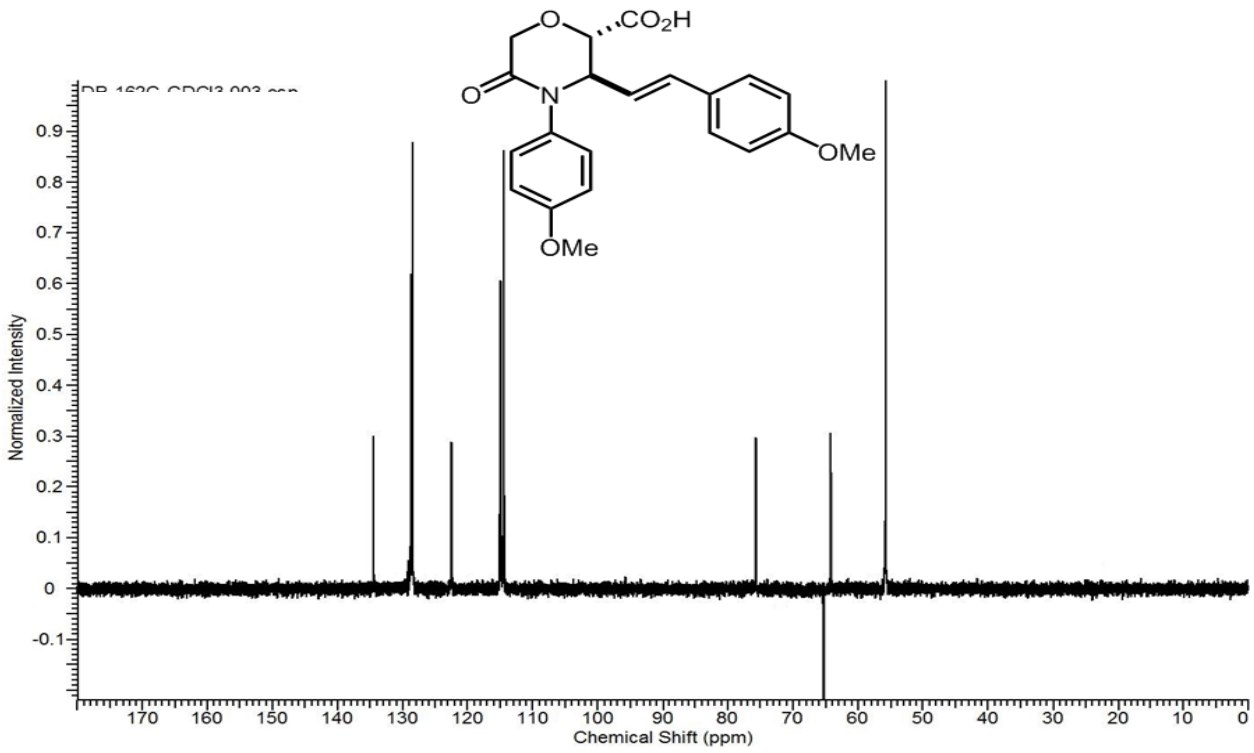
Spectrum 1-29: DEPT-135 NMR spectrum of **5d2.**



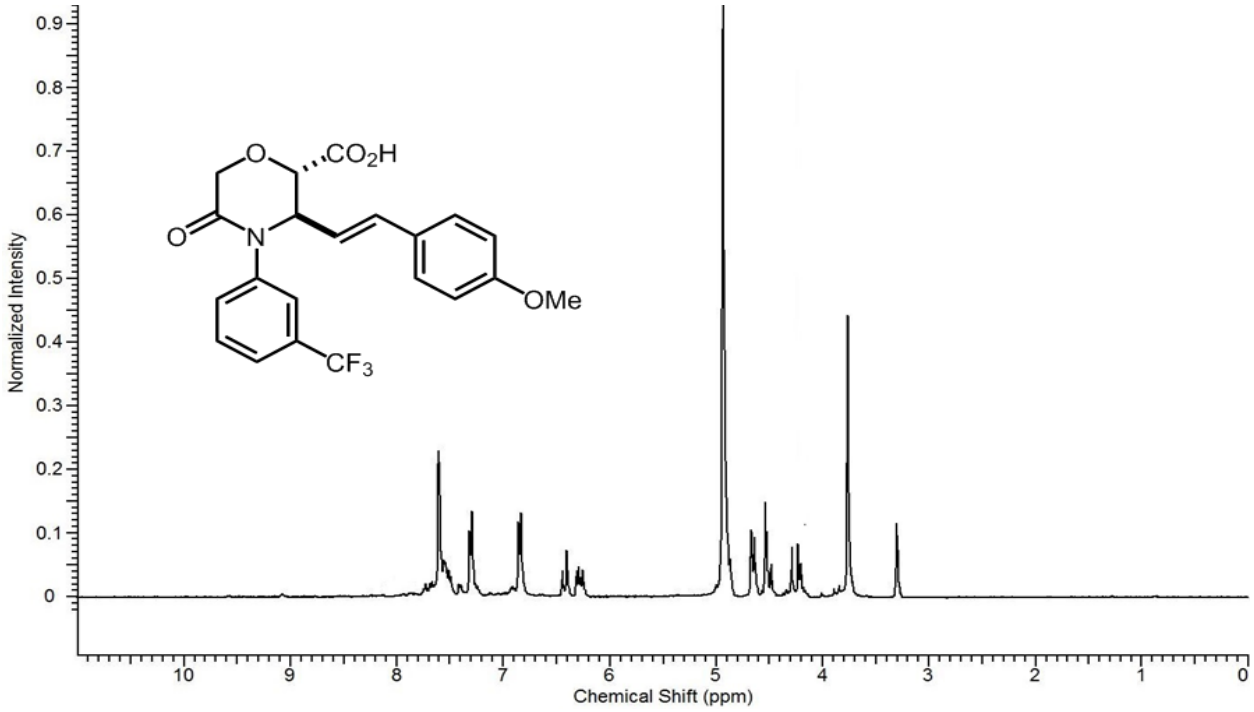
Spectrum 1-30: ^{1}H NMR spectrum of **5e1.**



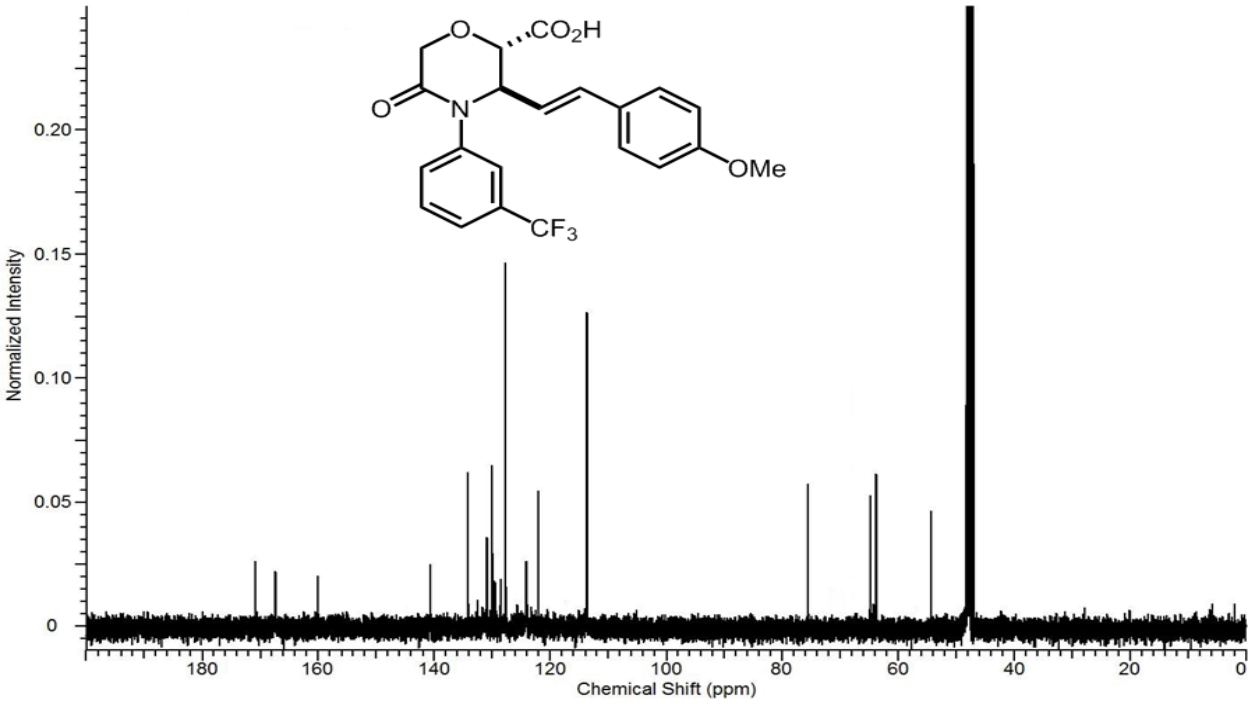
Spectrum 1-31: ^{13}C NMR spectrum of **5e1.**



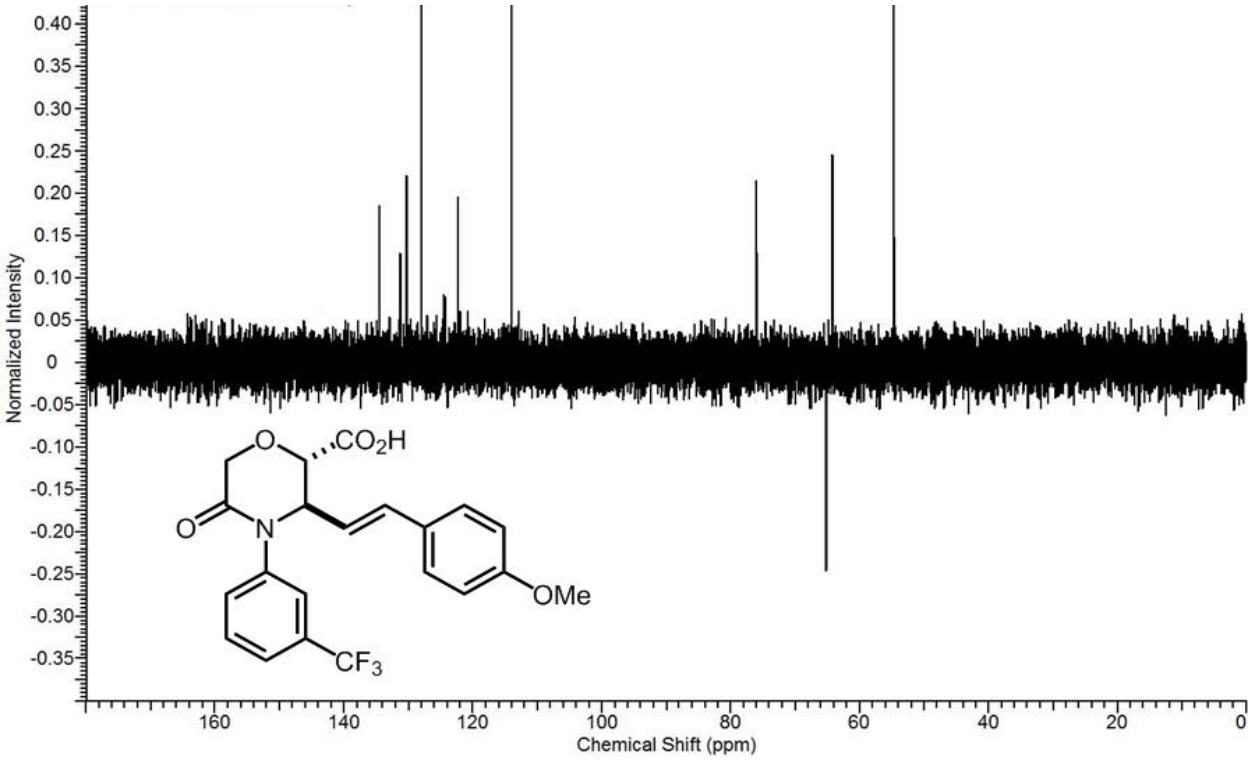
Spectrum 1-32: DEPT-135 NMR spectrum of **5e1.**



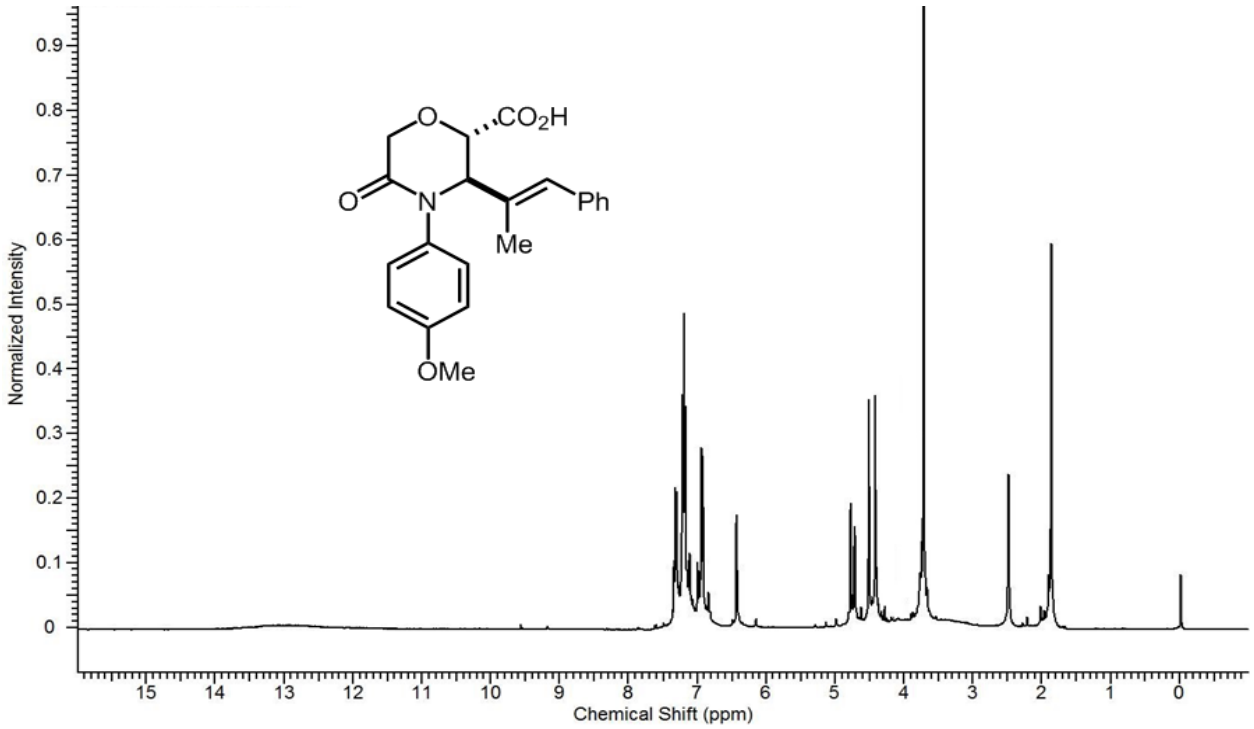
Spectrum 1-33: ^{1}H NMR spectrum of **5f1.**



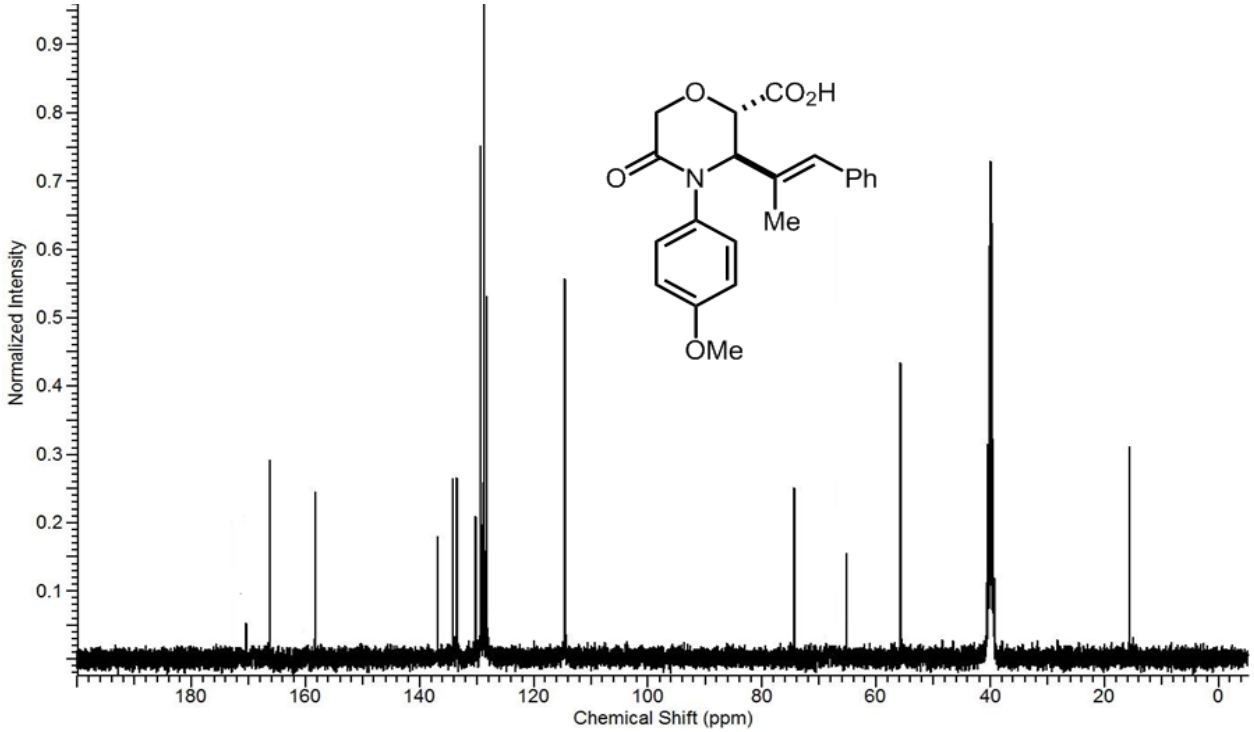
Spectrum 1-34: ^{13}C NMR spectrum of **5f1.**



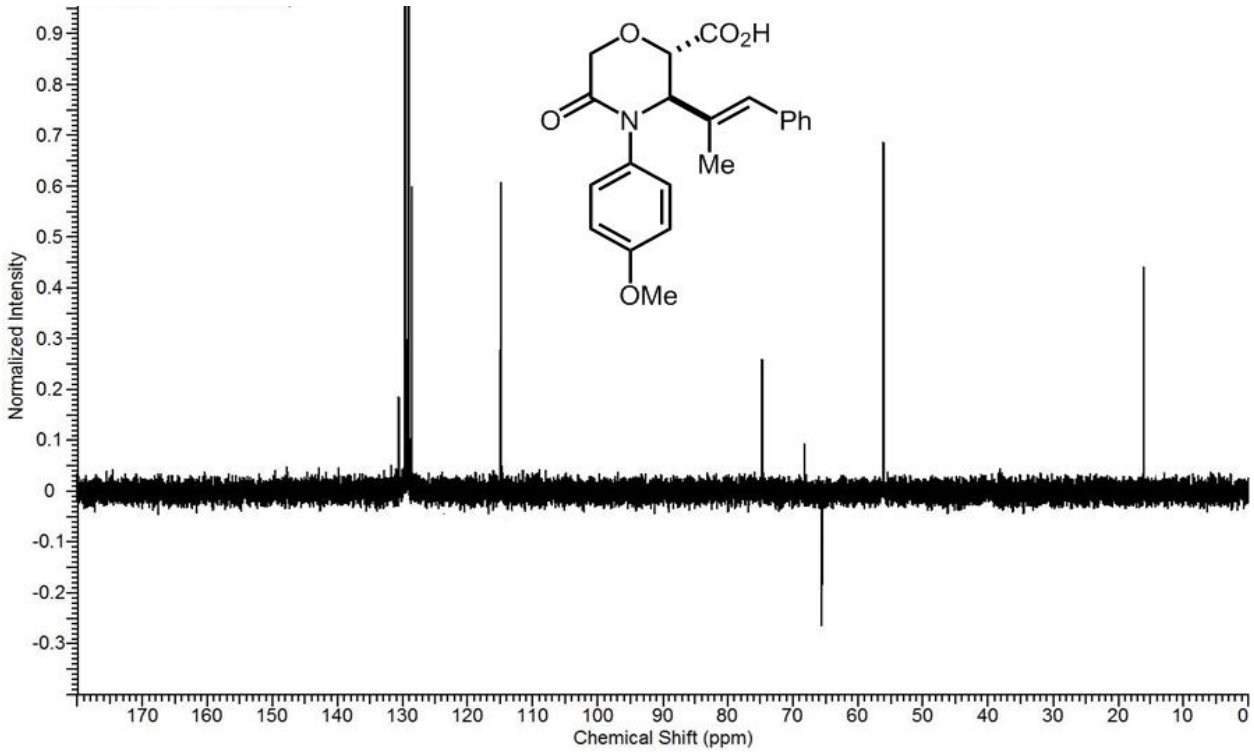
Spectrum 1-35: DEPT-135 NMR spectrum of **5f1.**



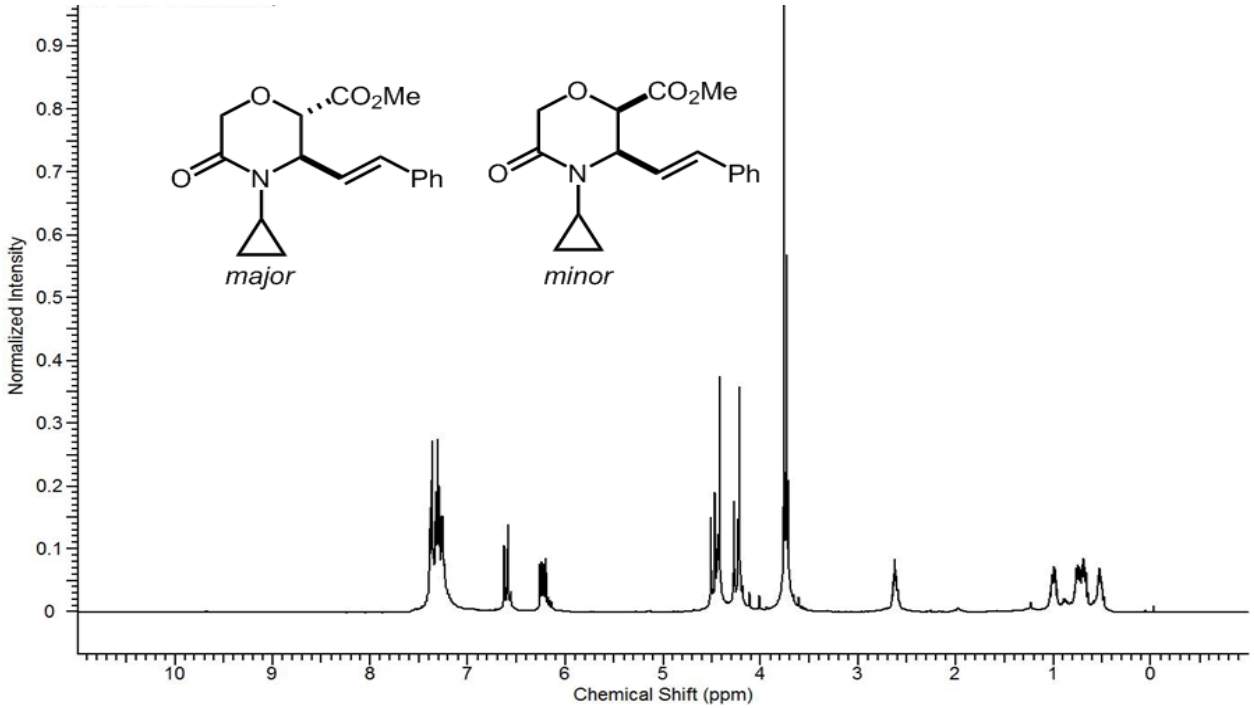
Spectrum 1-36: ^{1}H NMR spectrum of **5g1.**



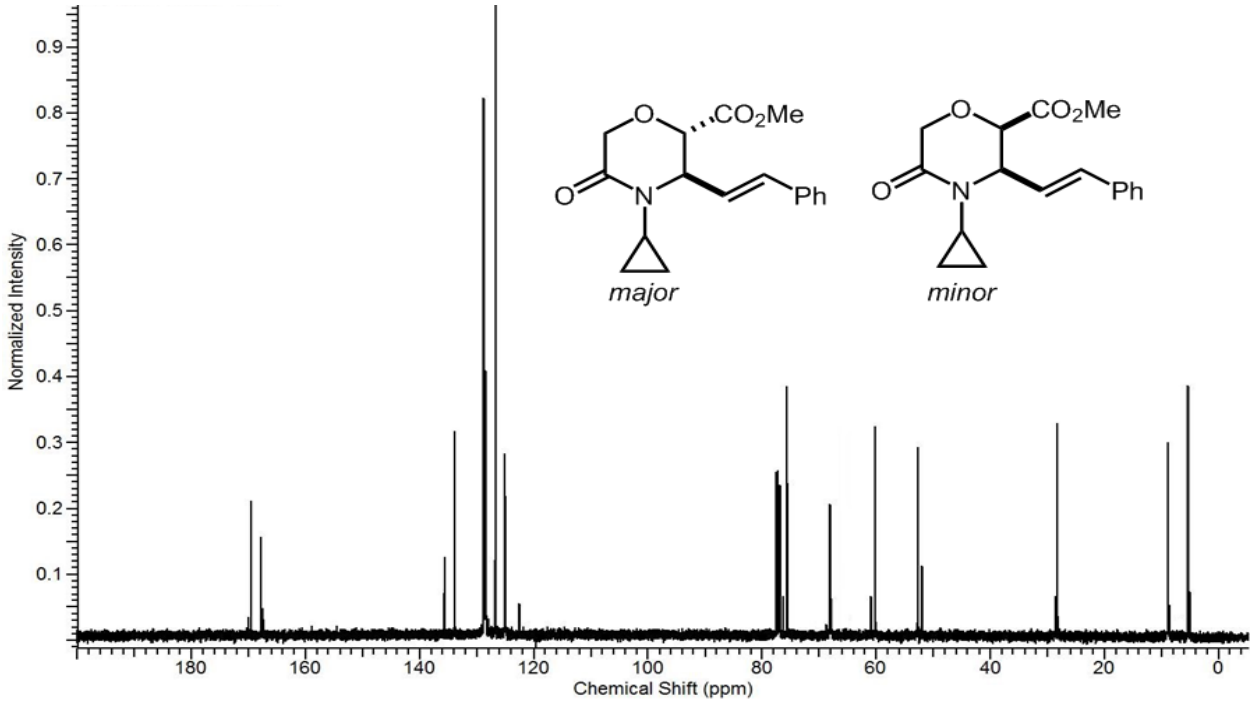
Spectrum 1-37: ^{13}C NMR spectrum of **5g1.**



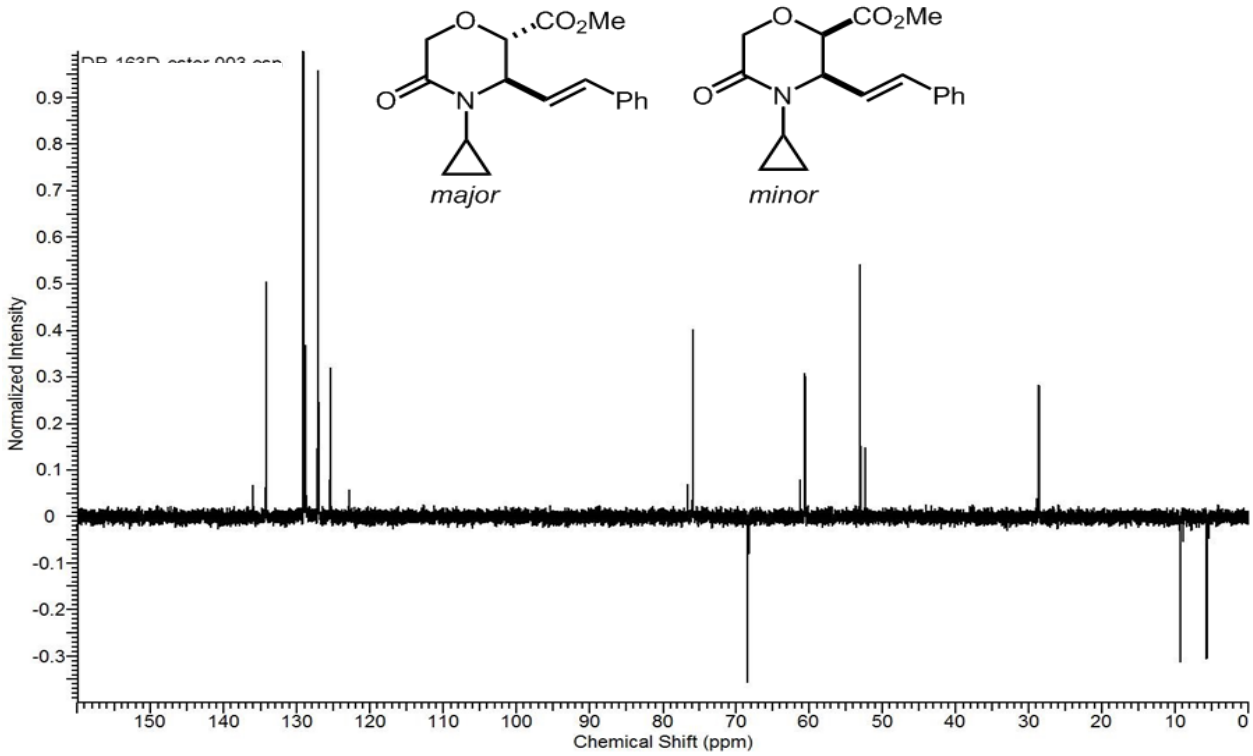
Spectrum 1-38: DEPT-135 NMR spectrum of **5g1.**



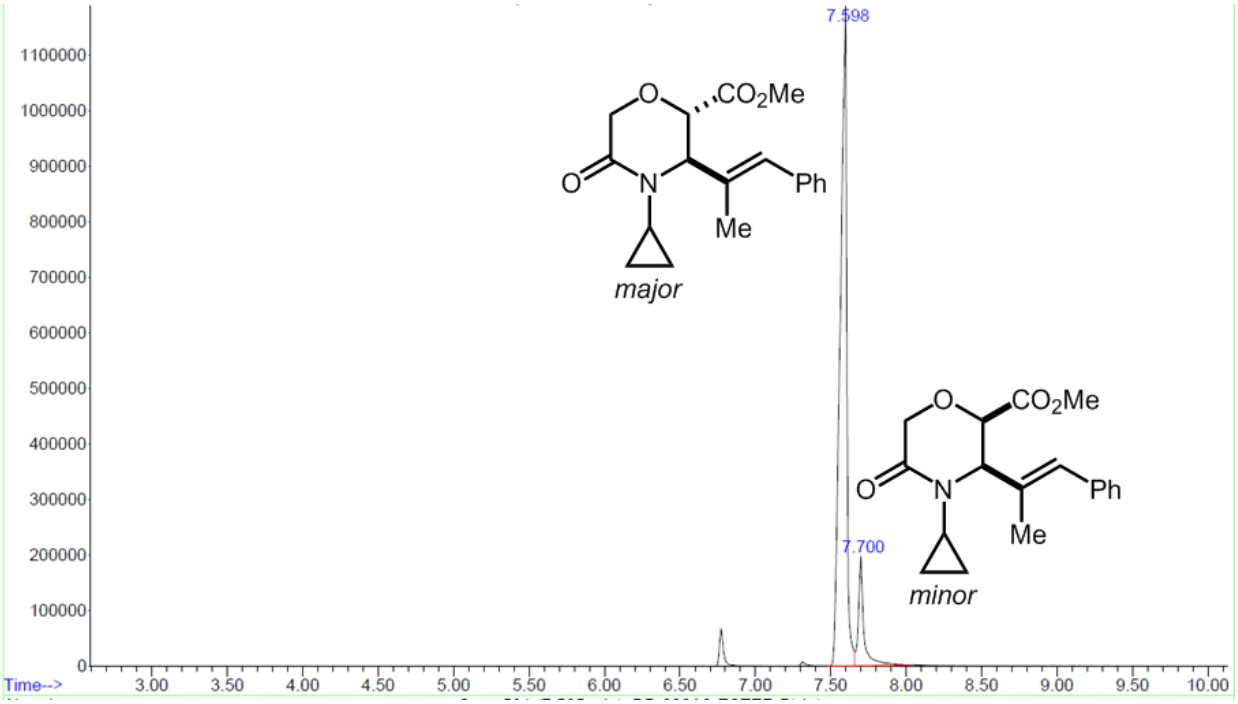
Spectrum 1-39: ^{1}H NMR spectrum of **5h2 major and minor.**



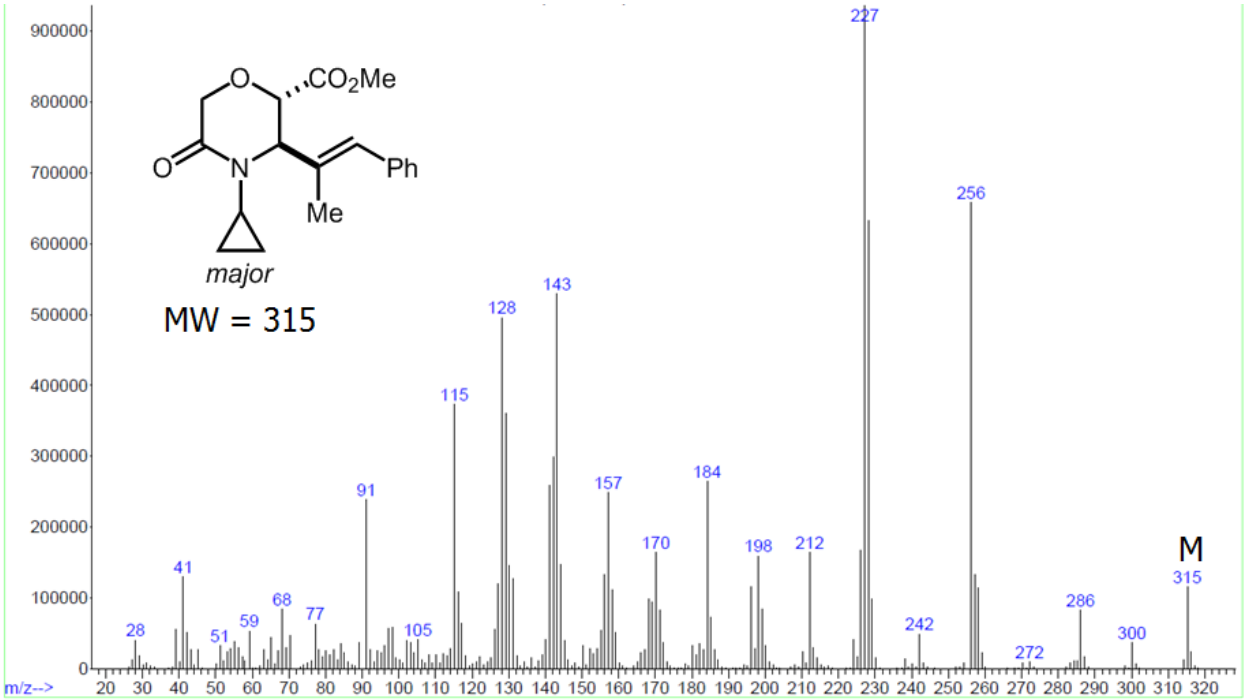
Spectrum 1-40: ^{13}C NMR spectrum of **5h2 major and minor.**



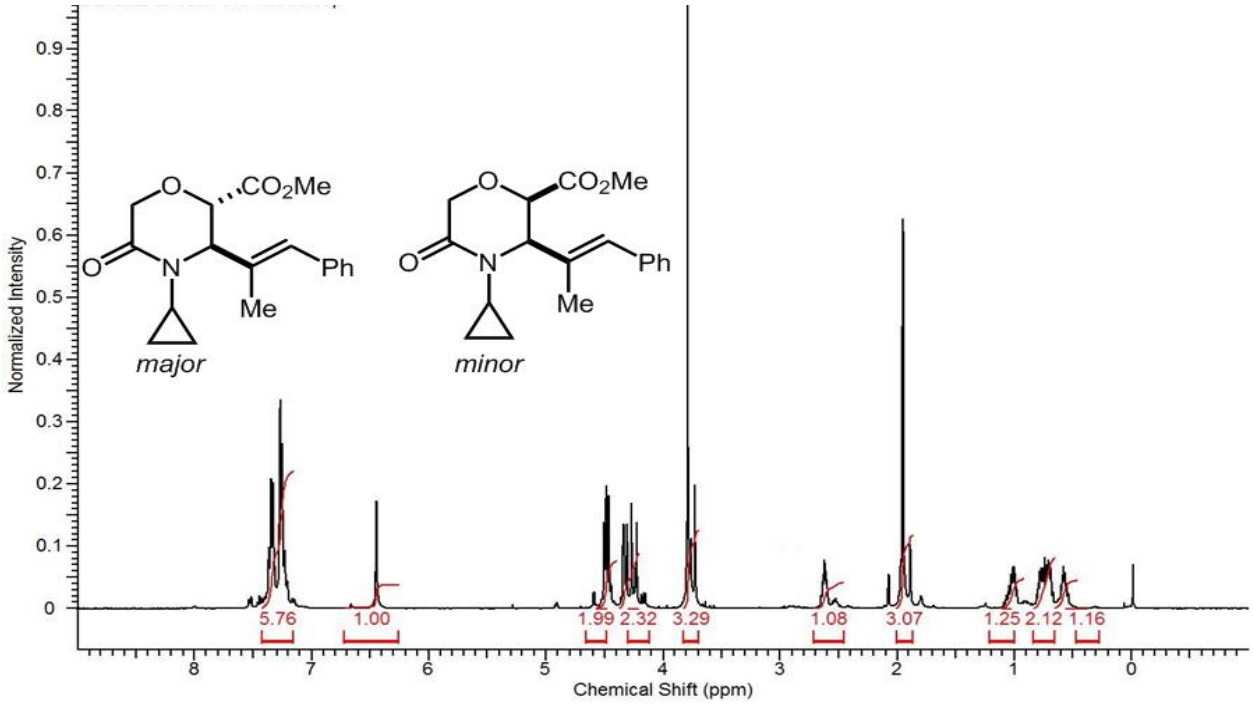
Spectrum 1-41: DEPT-135 NMR spectrum of **5h2 major and minor.**



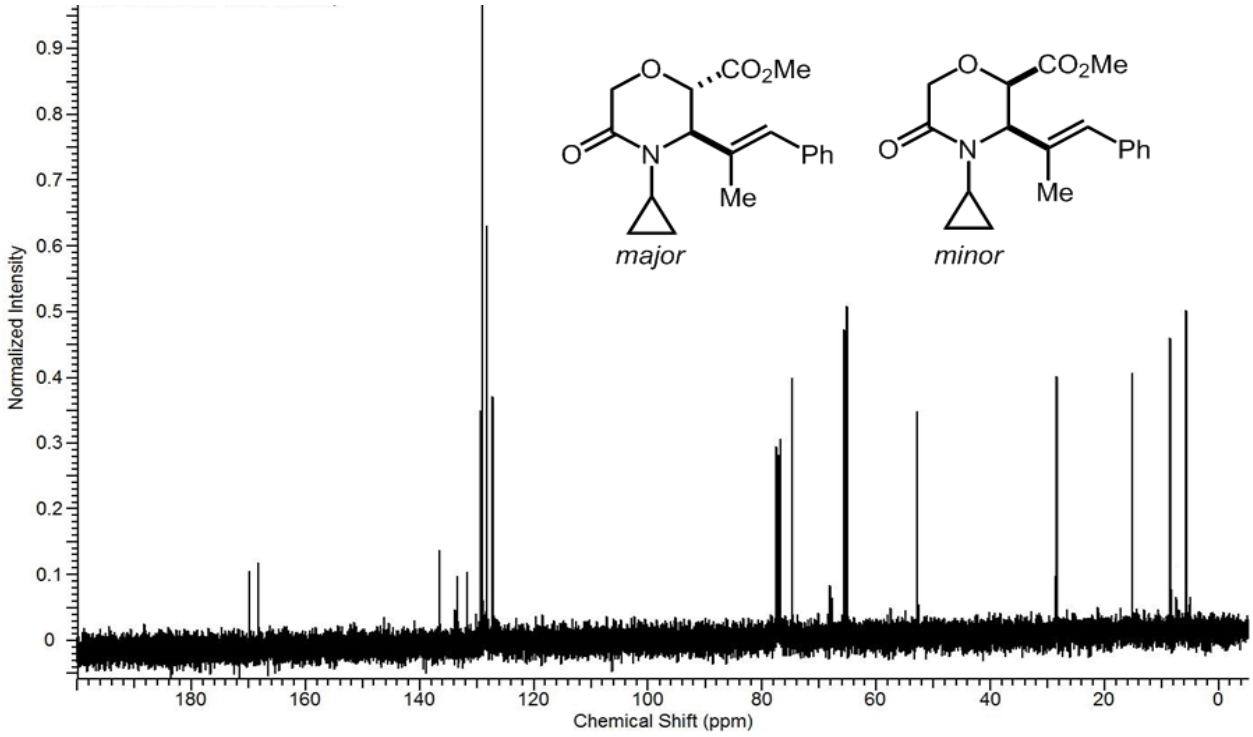
Spectrum 1-42: GC spectrum of **5i2 major and minor.**



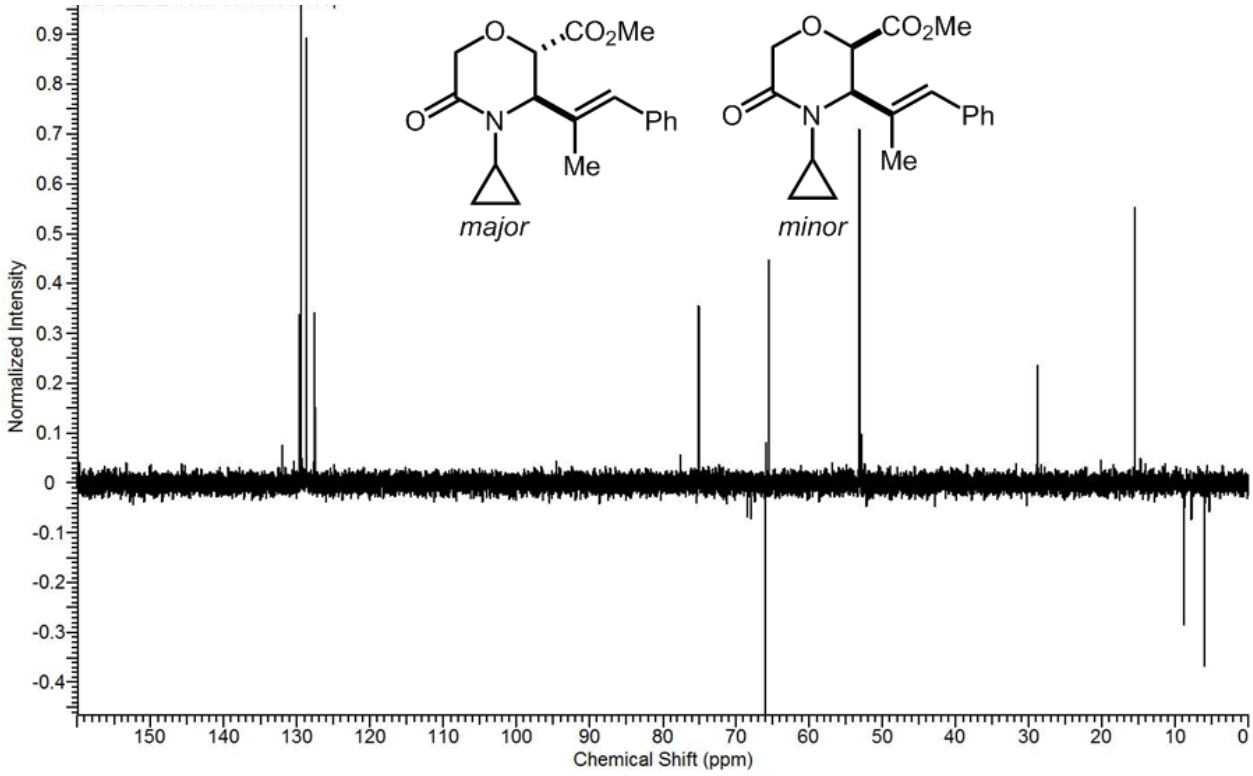
Spectrum 1-43: MS spectrum of **5i2 major.**



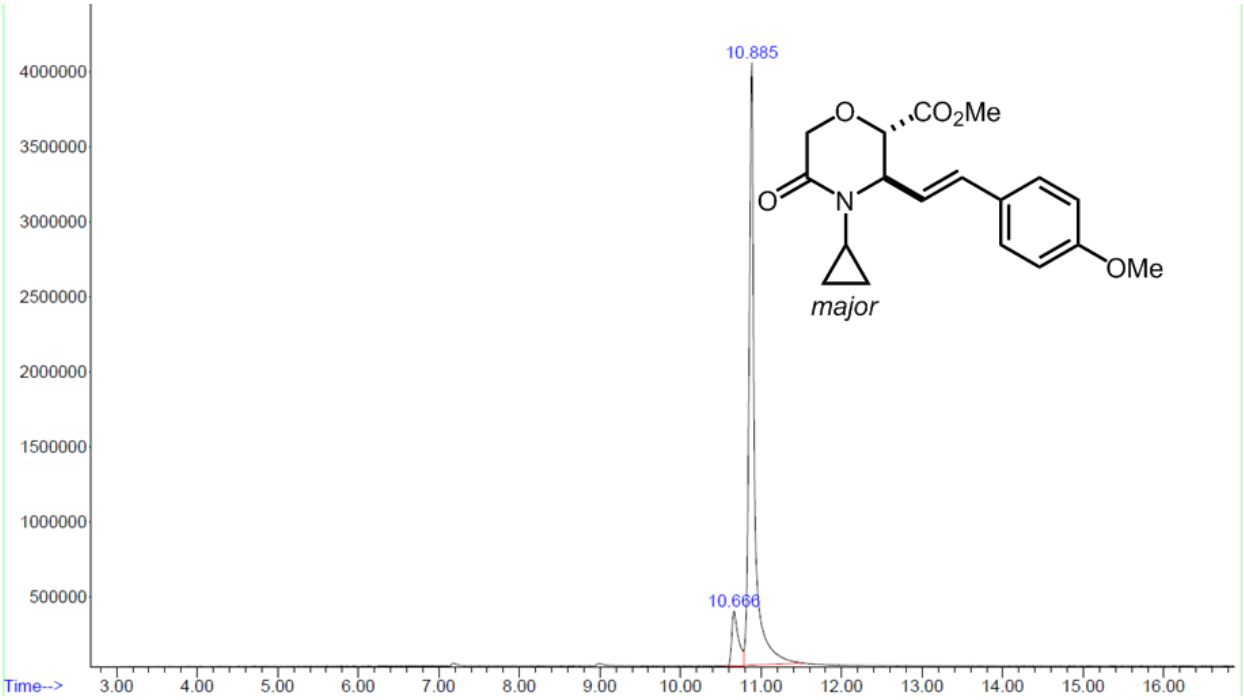
Spectrum 1-44: ^{1}H NMR spectrum of **5i2 major and minor.**



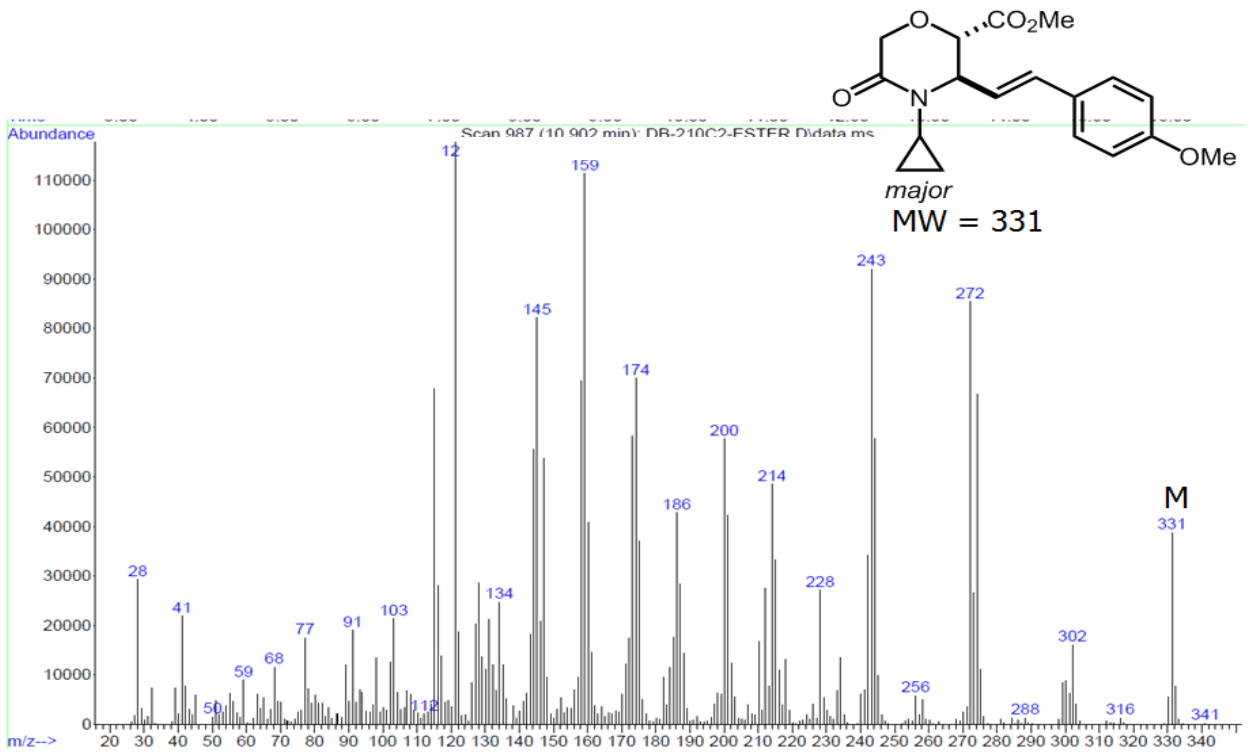
Spectrum 1-45: ^{13}C NMR spectrum of **5i2 major and minor.**



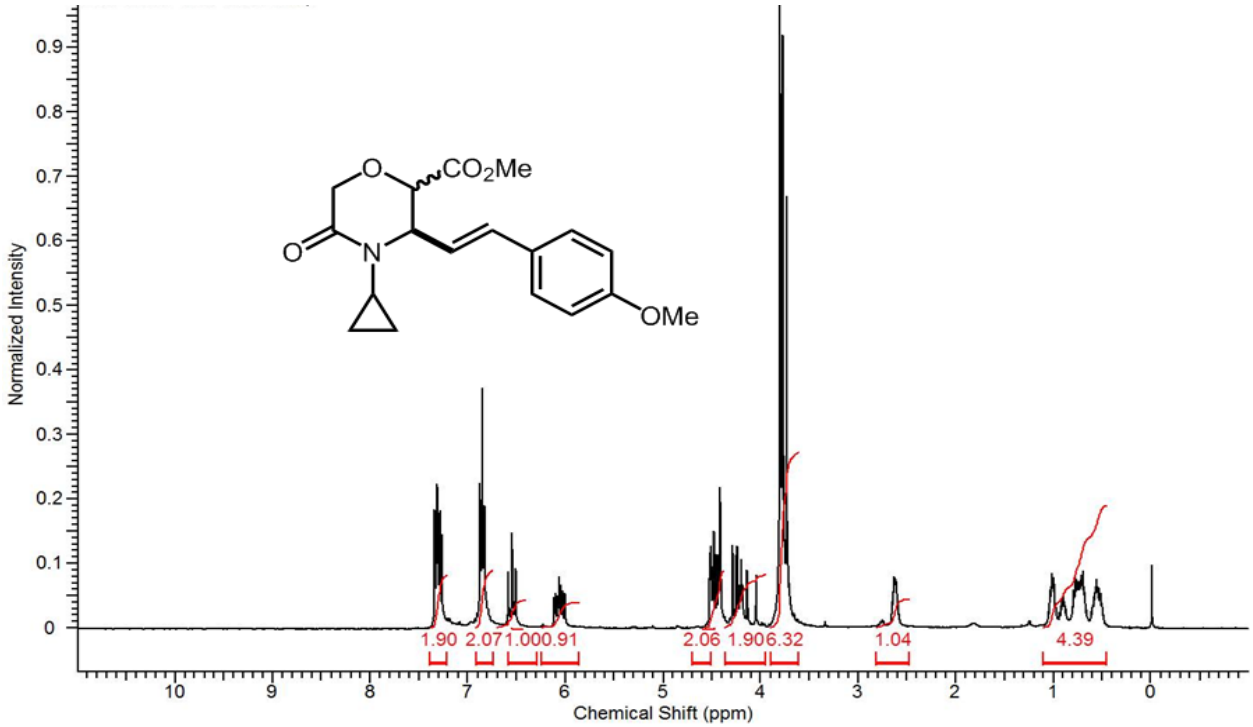
Spectrum 1-46: DEPT-135 NMR spectrum of **5i2 major and minor.**



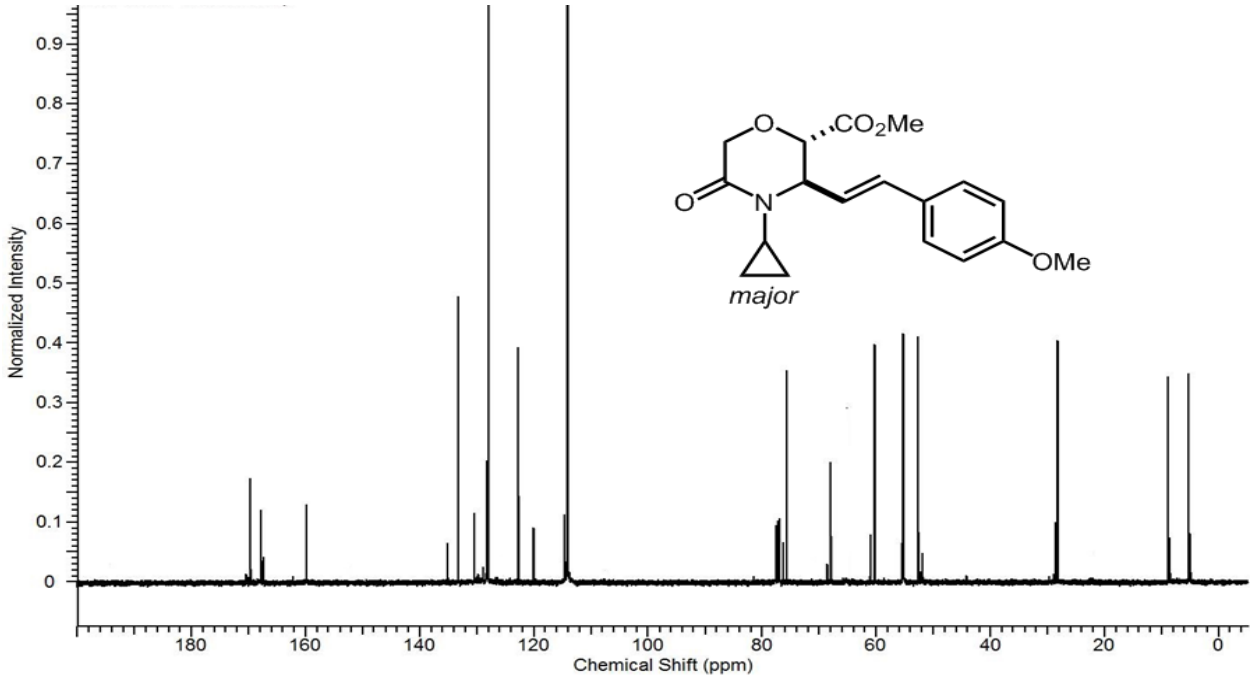
Spectrum 1-47: GC spectrum of **5j2 major and minor.**



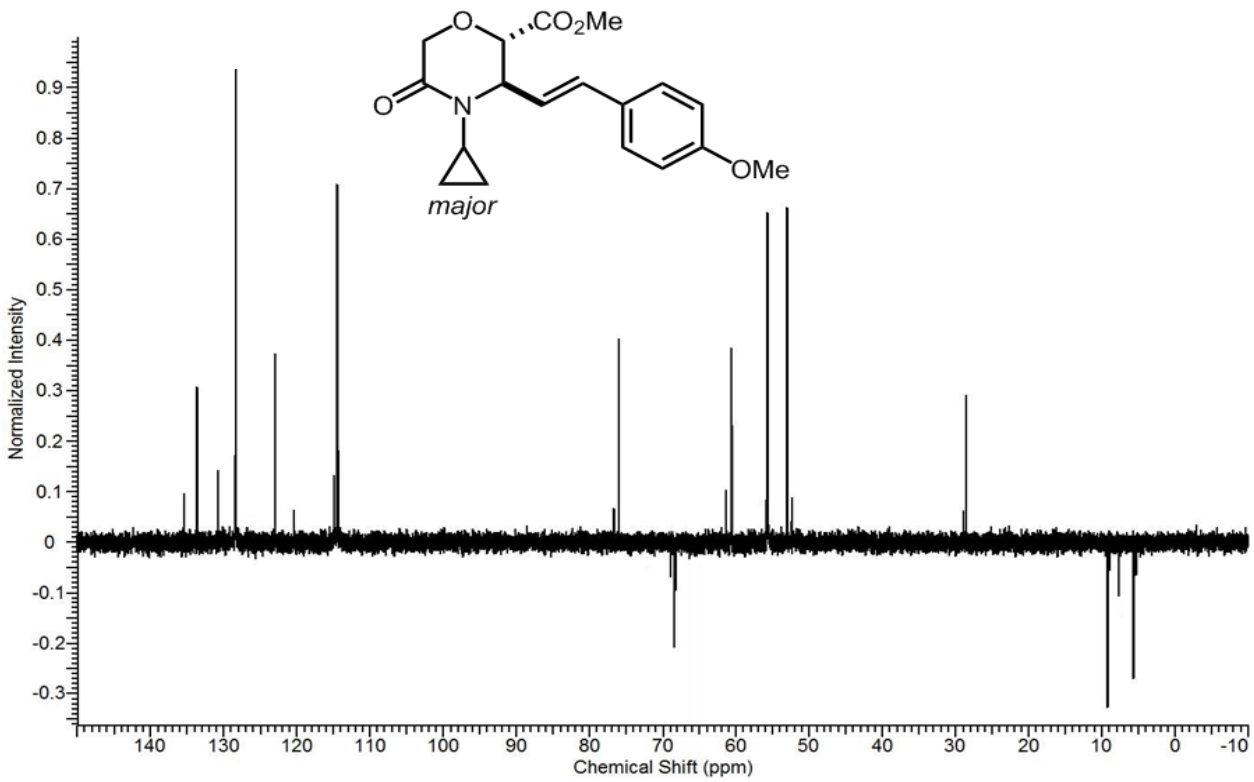
Spectrum 1-48: MS spectrum of **5j2 major.**



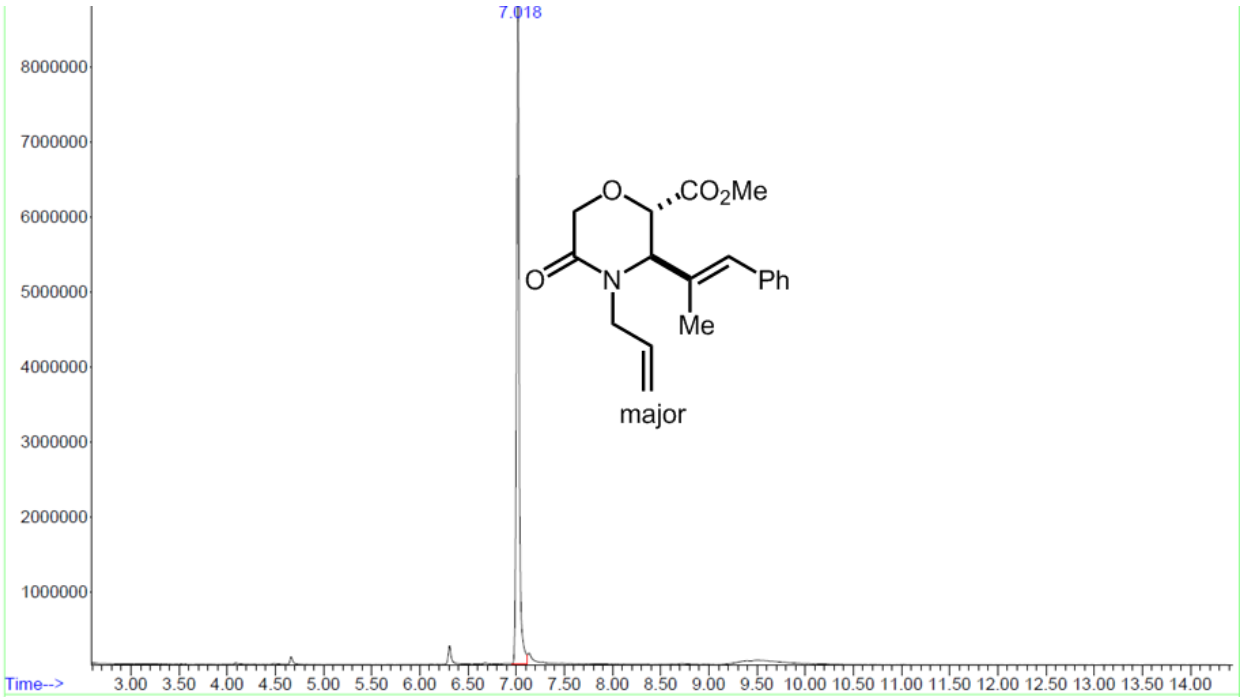
Spectrum 1-49: ^{1}H NMR spectrum of **5j2 major and minor.**



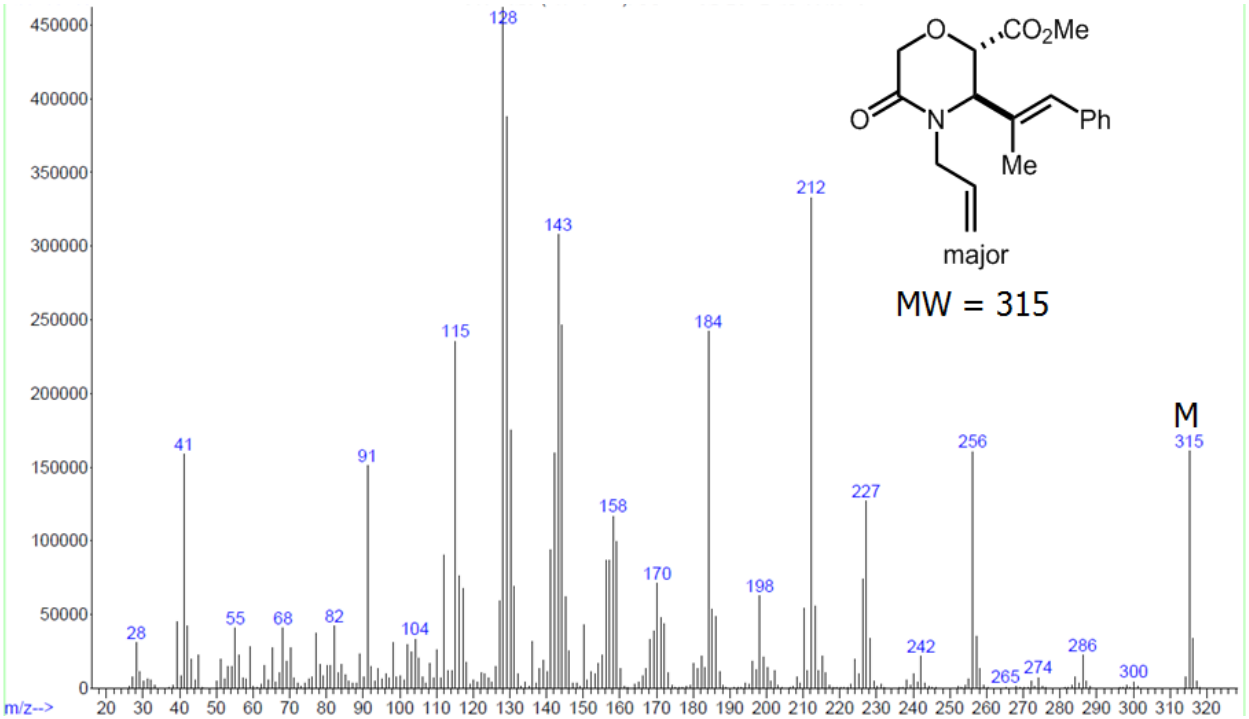
Spectrum 1-50: ^{13}C NMR spectrum of **5j2 major and minor.**



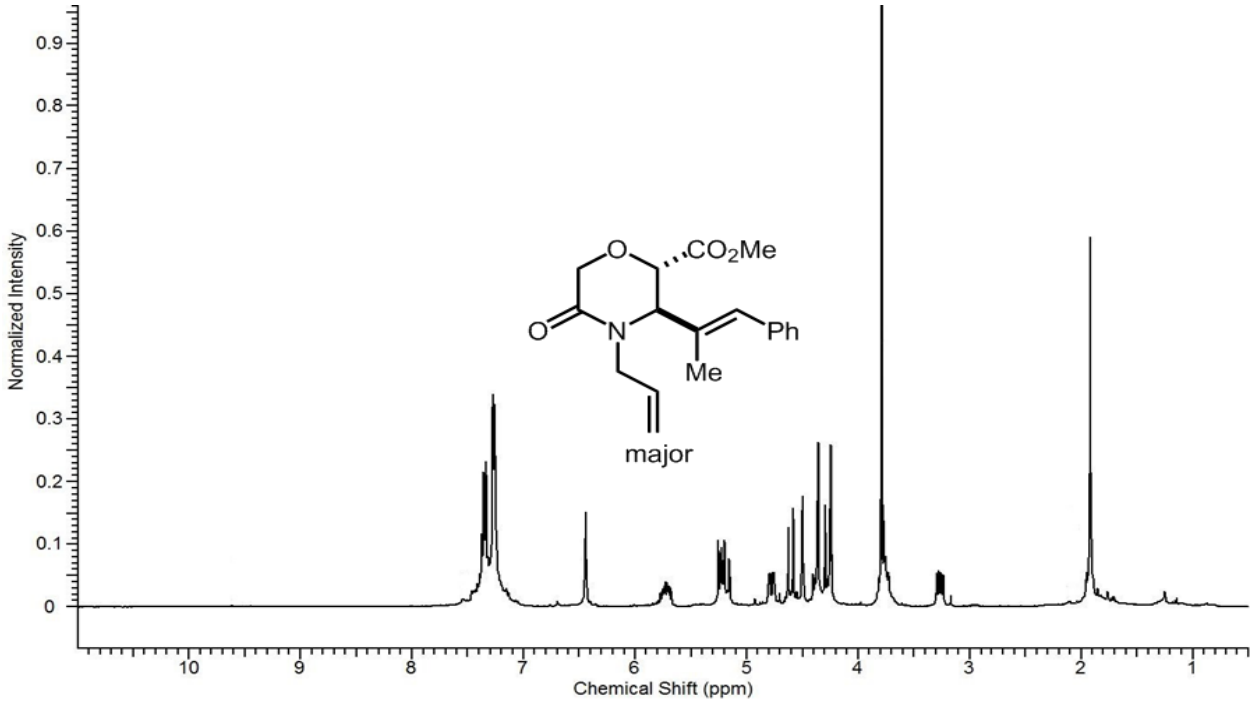
Spectrum 1-51: DEPT-135 NMR spectrum of **5j2 major and minor.**



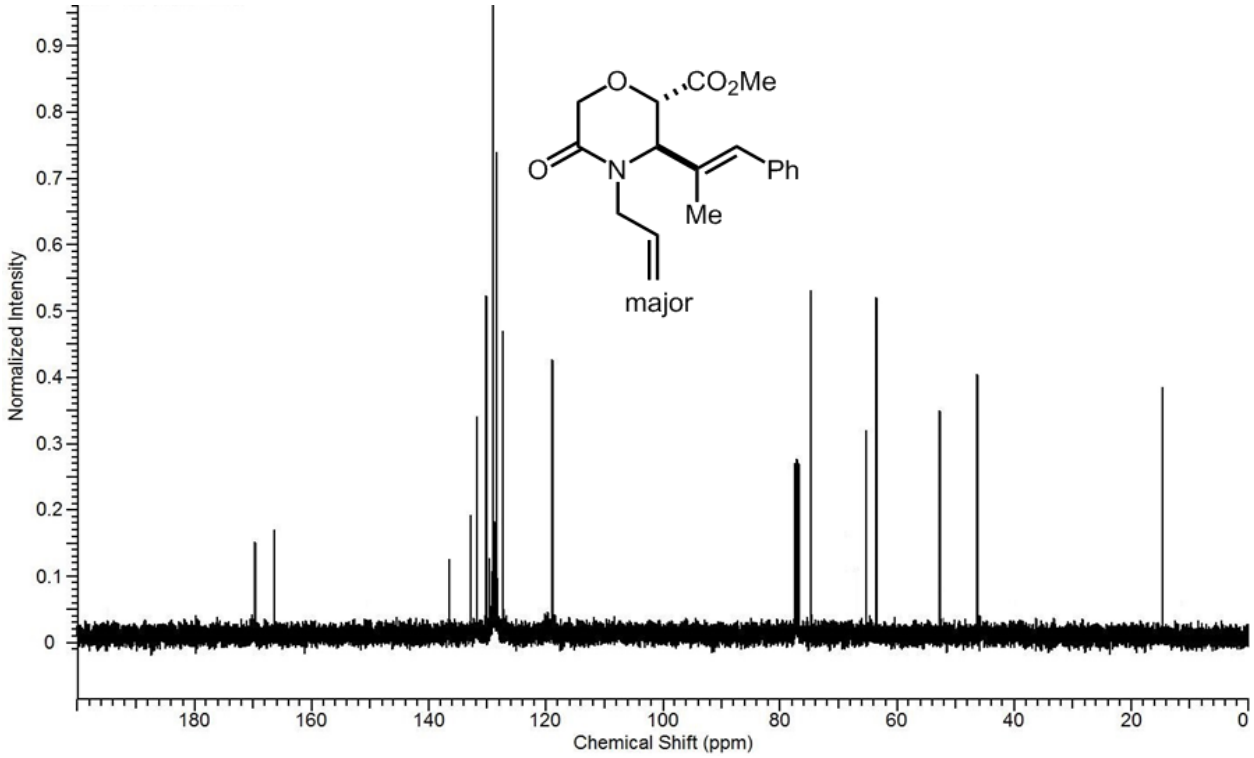
Spectrum 1-52: GC spectrum of **5k2.**



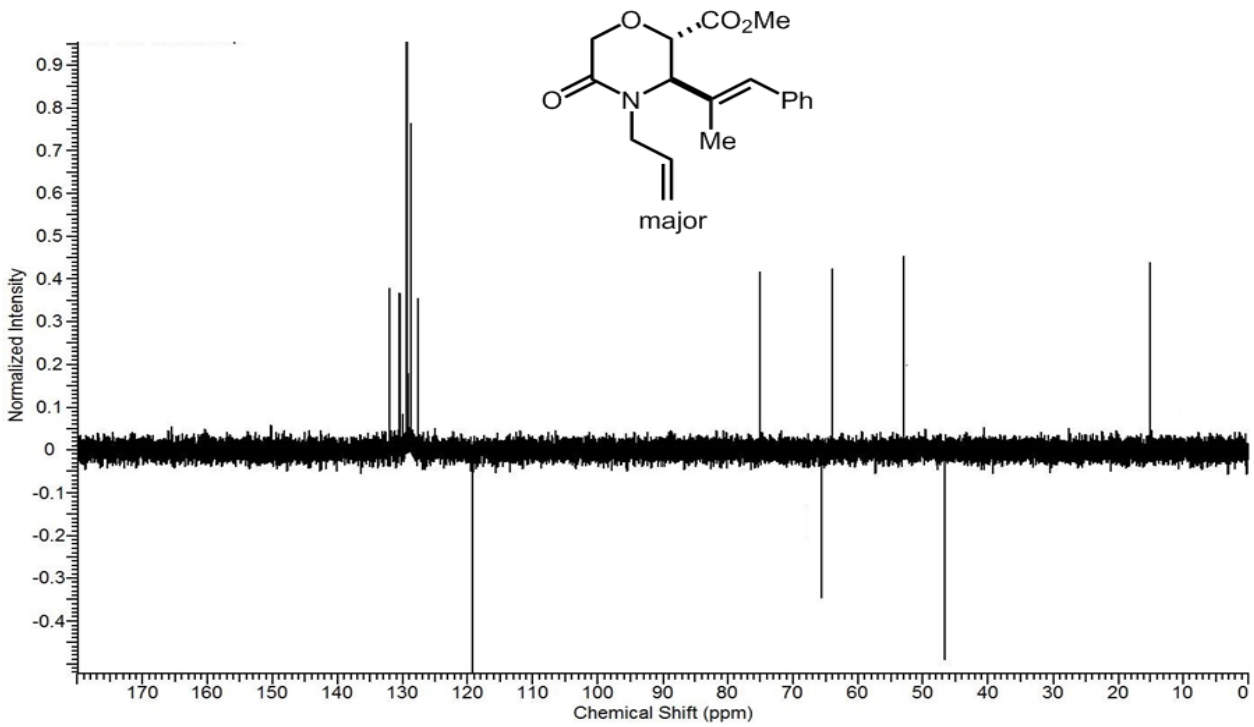
Spectrum 1-53: MS spectrum of **5k2.**



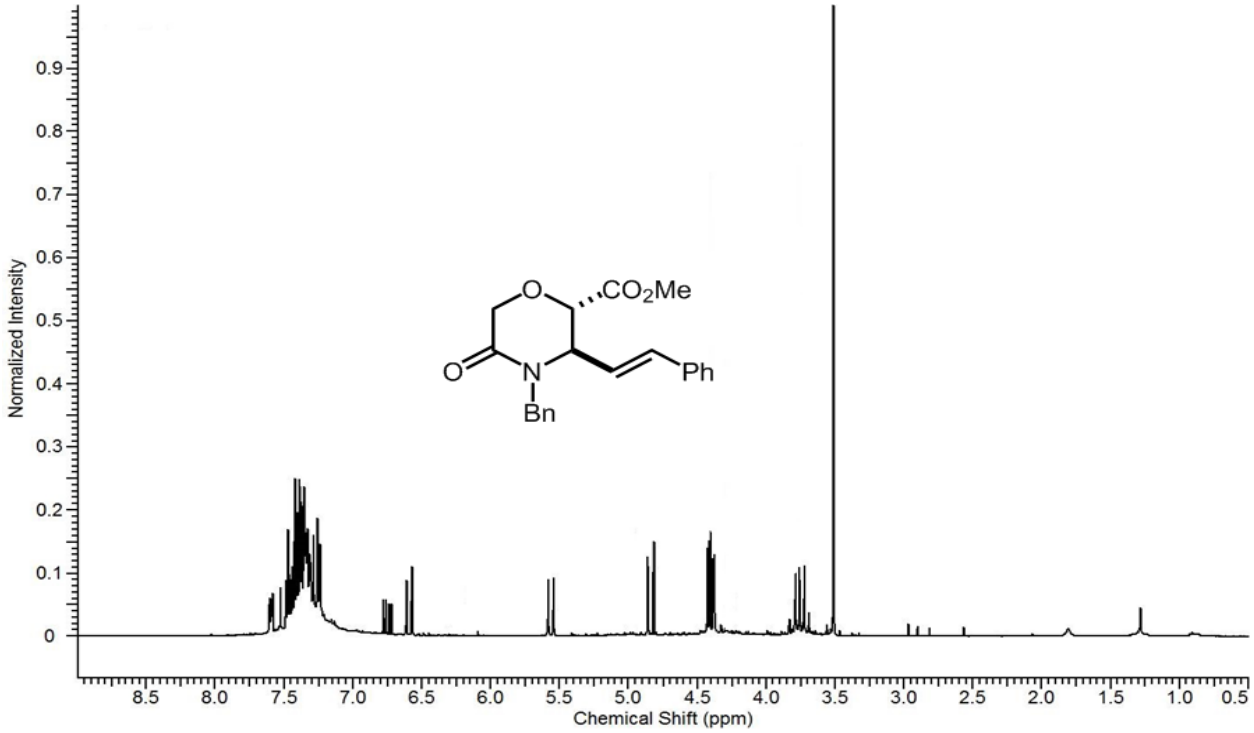
Spectrum 1-54: ^{1}H NMR spectrum of **5k2.**



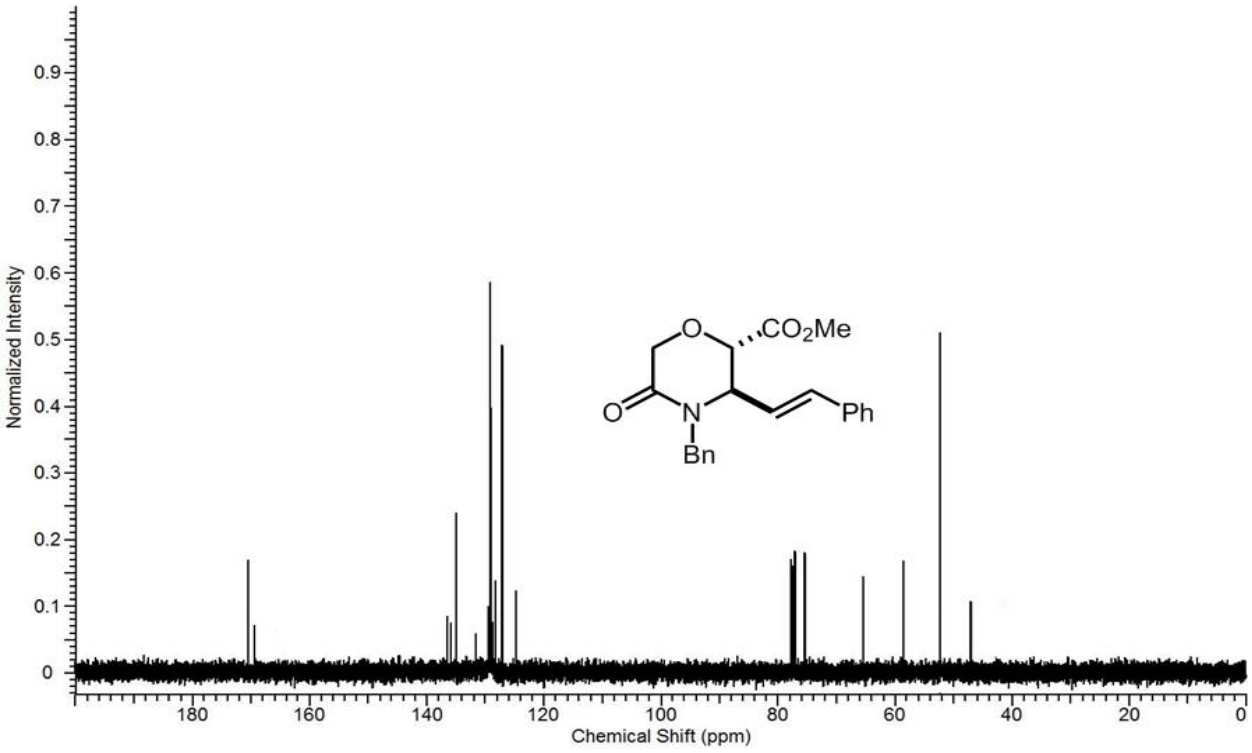
Spectrum 1-55: ^{13}C NMR spectrum of **5k2.**



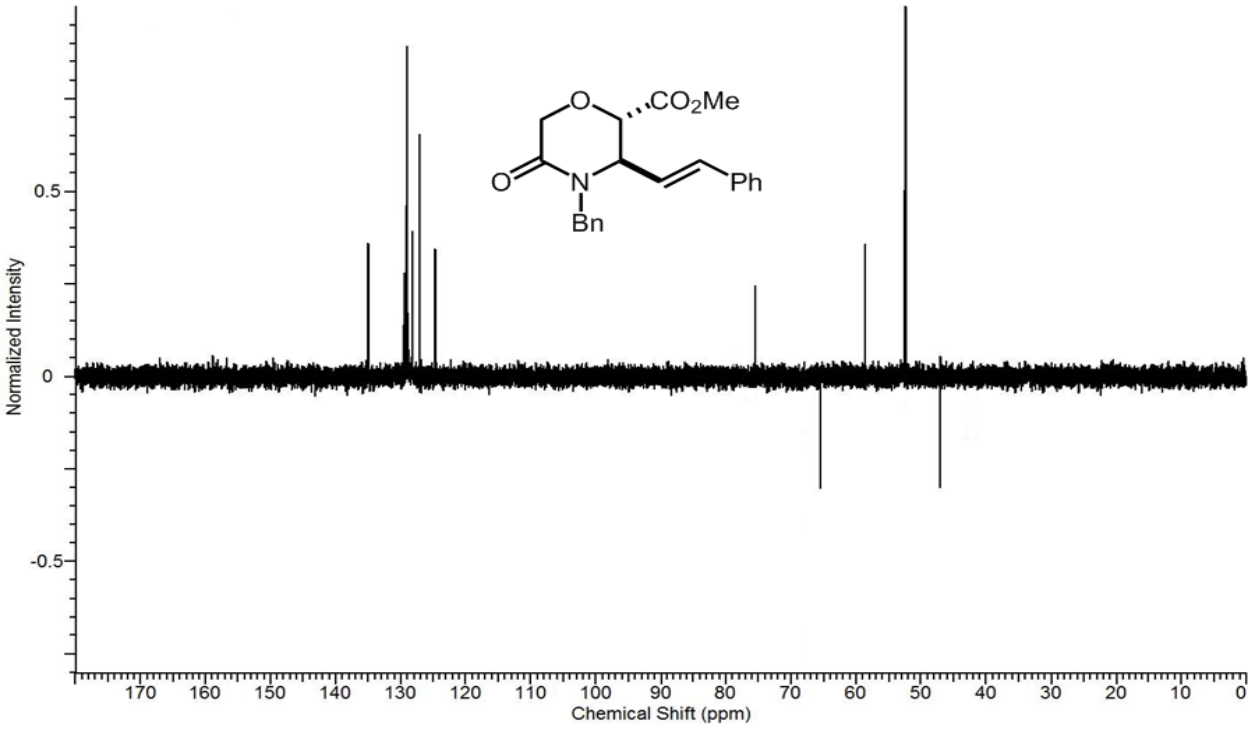
Spectrum 1-56: DEPT-135 spectrum of **5k2.**



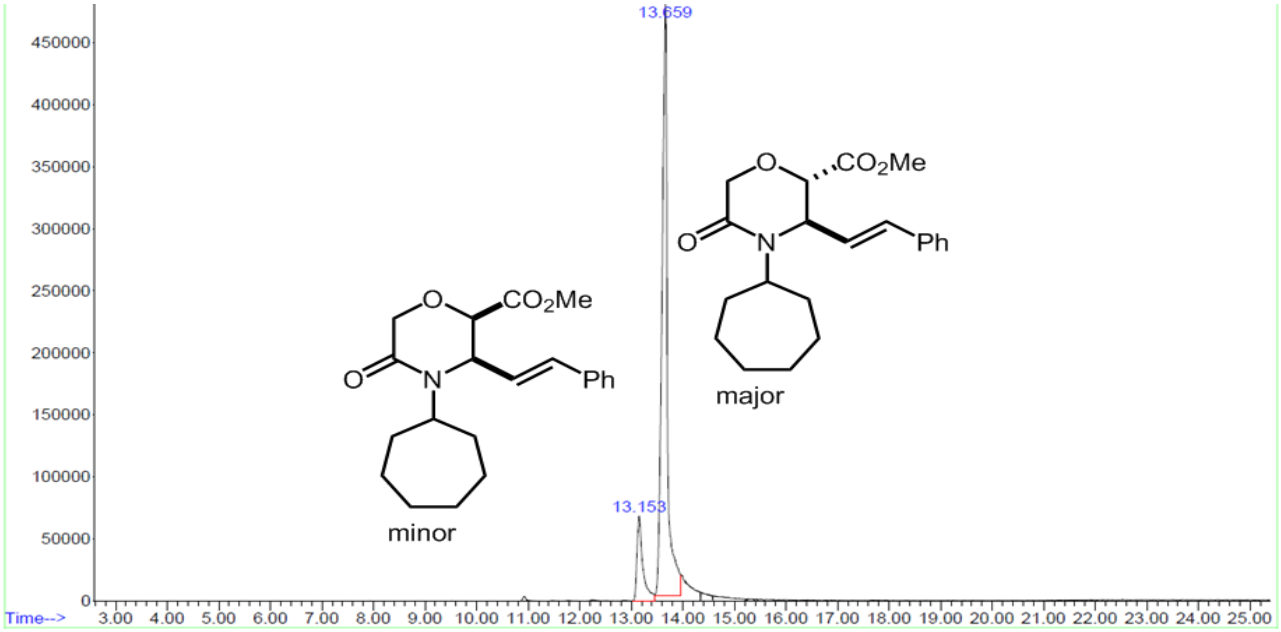
Spectrum 1-57: ^{1}H NMR spectrum of **5l2.**



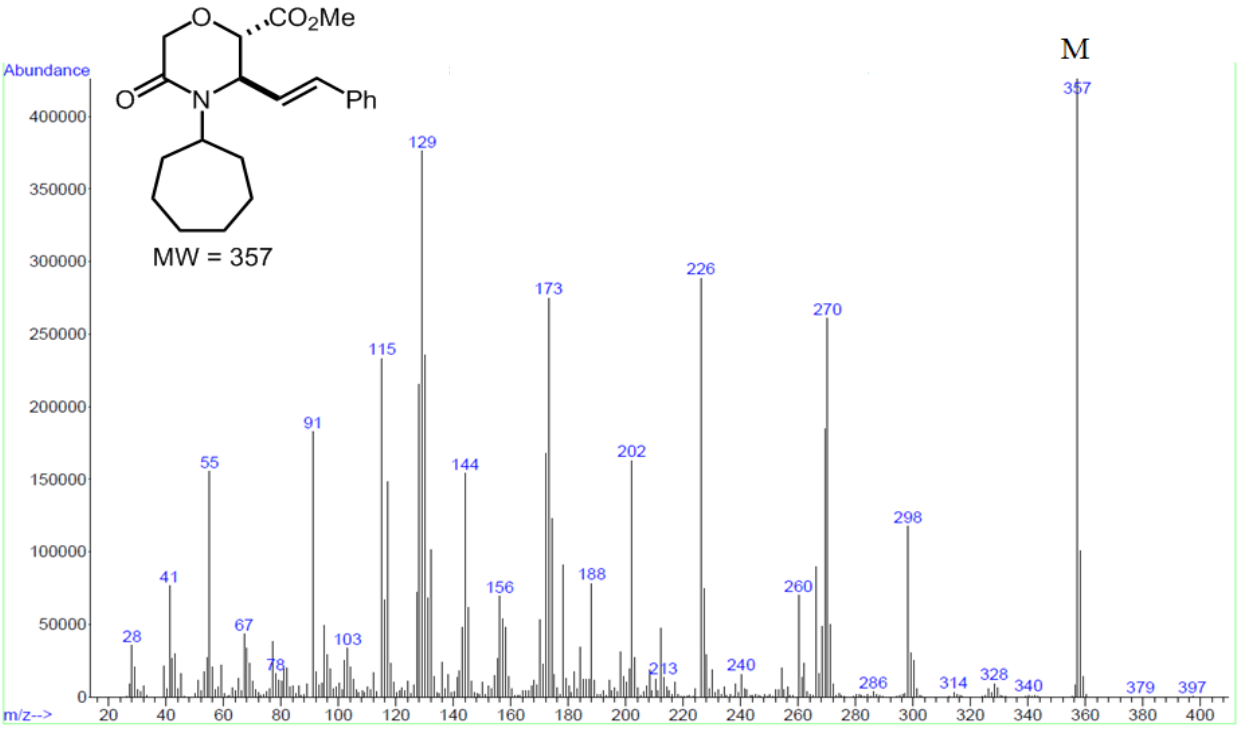
Spectrum 1-58: ^{13}C NMR spectrum of **5l2.**



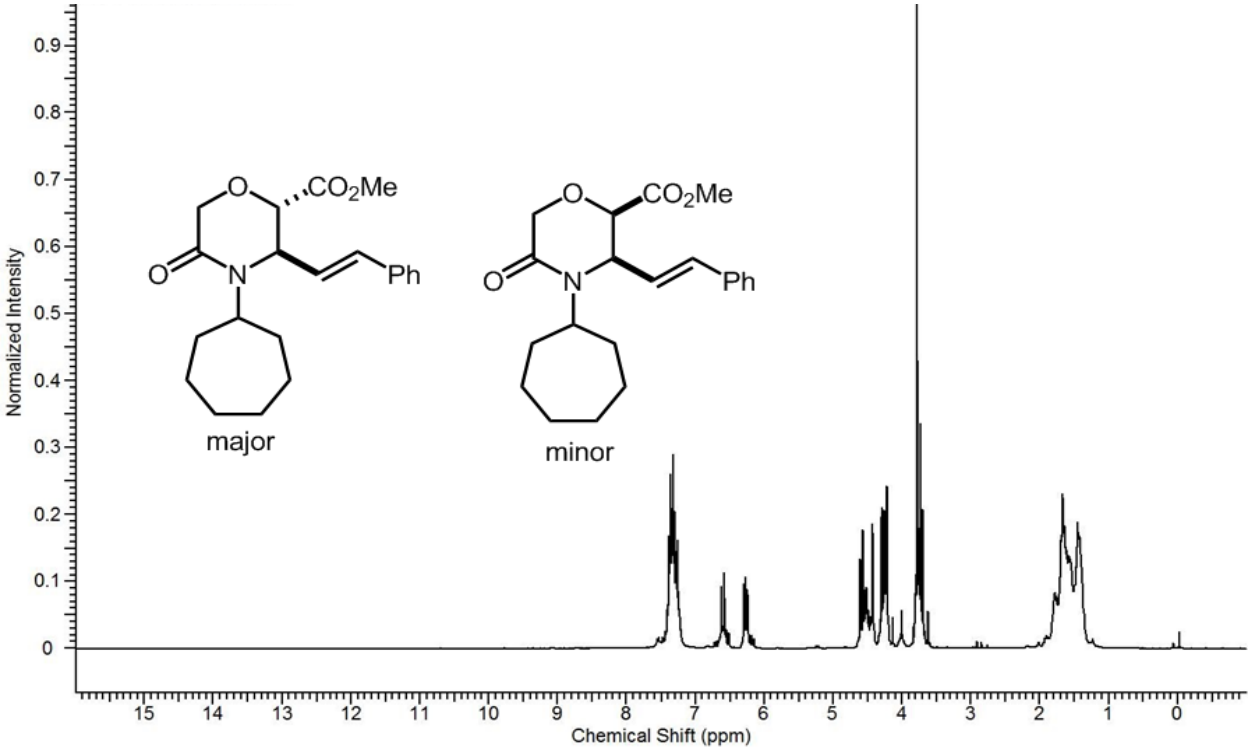
Spectrum 1-59: DEPT-135 NMR spectrum of **5l2.**



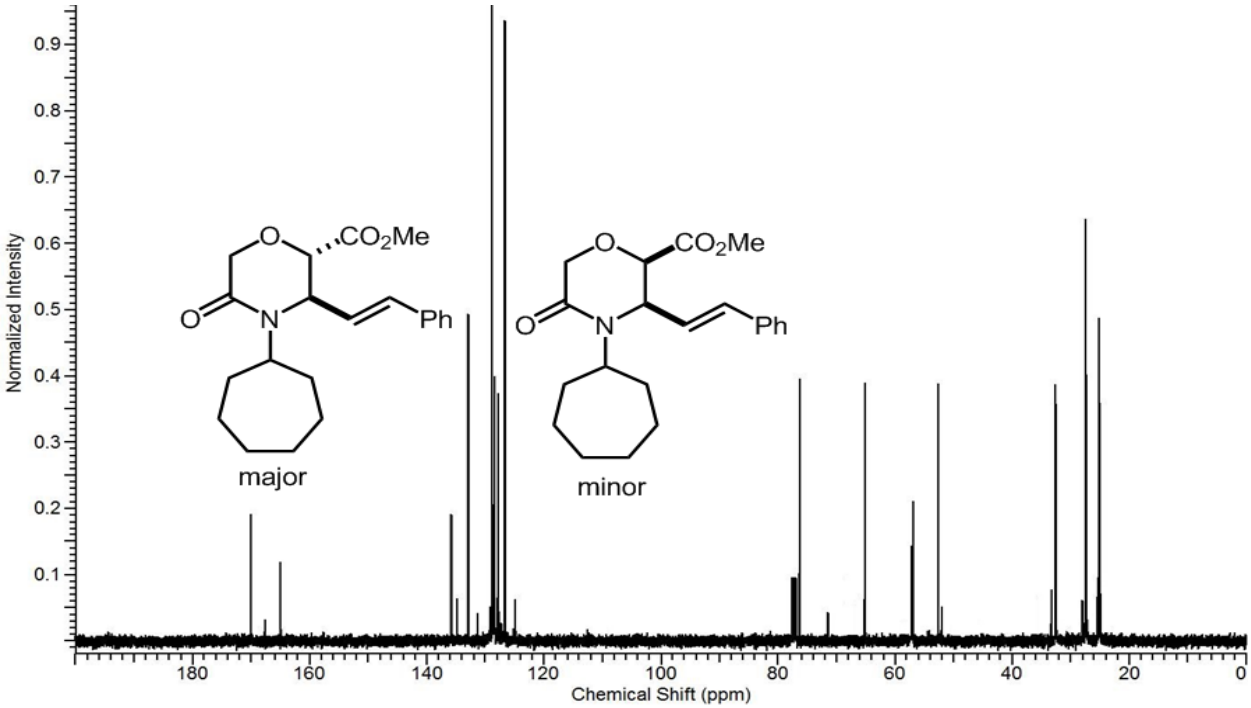
Spectrum 1-60: GC spectrum of **5m2 major and minor.**



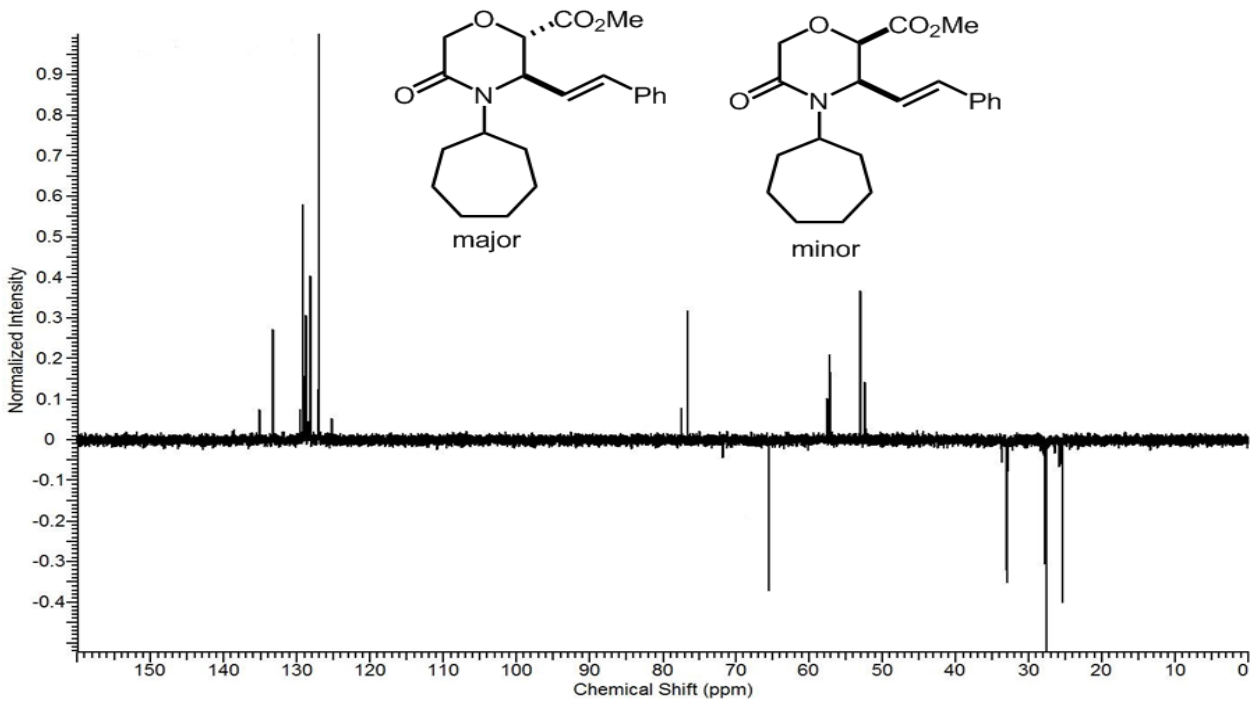
Spectrum 1-61: MS spectrum of **5m2 major.**



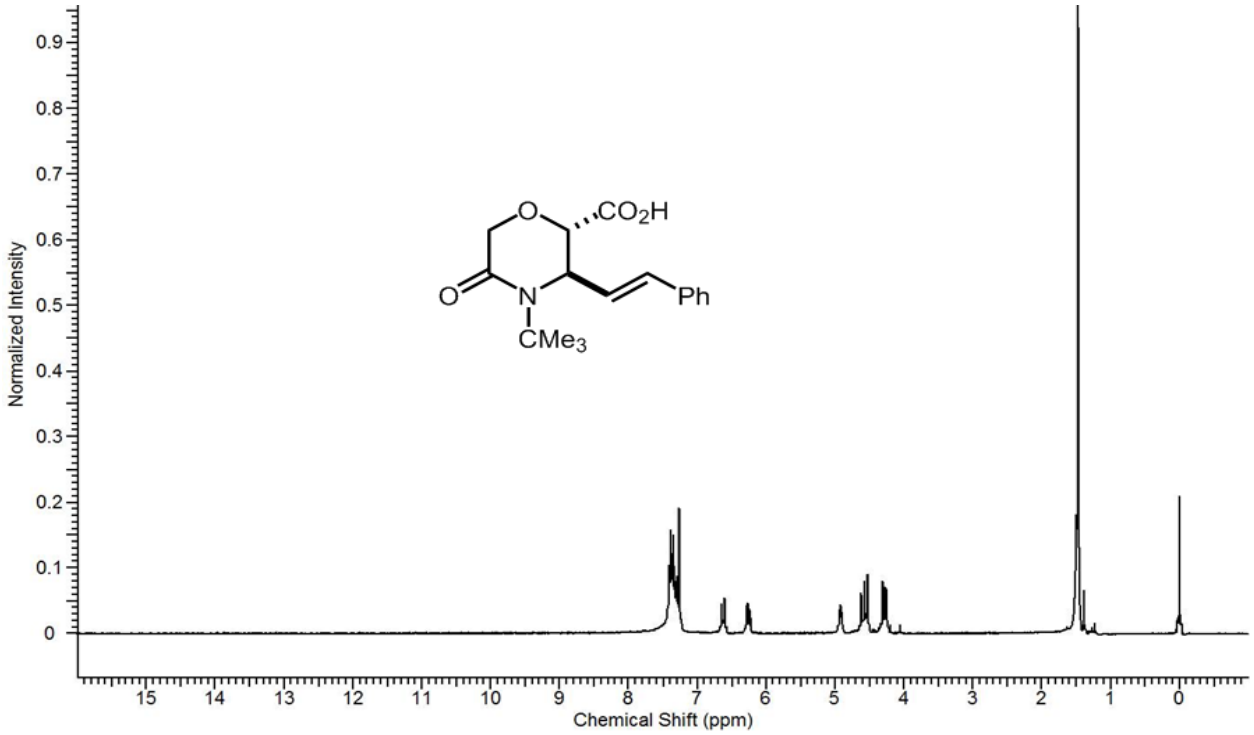
Spectrum 1-62: ^{1}H NMR spectrum of **5m2 major and minor.**



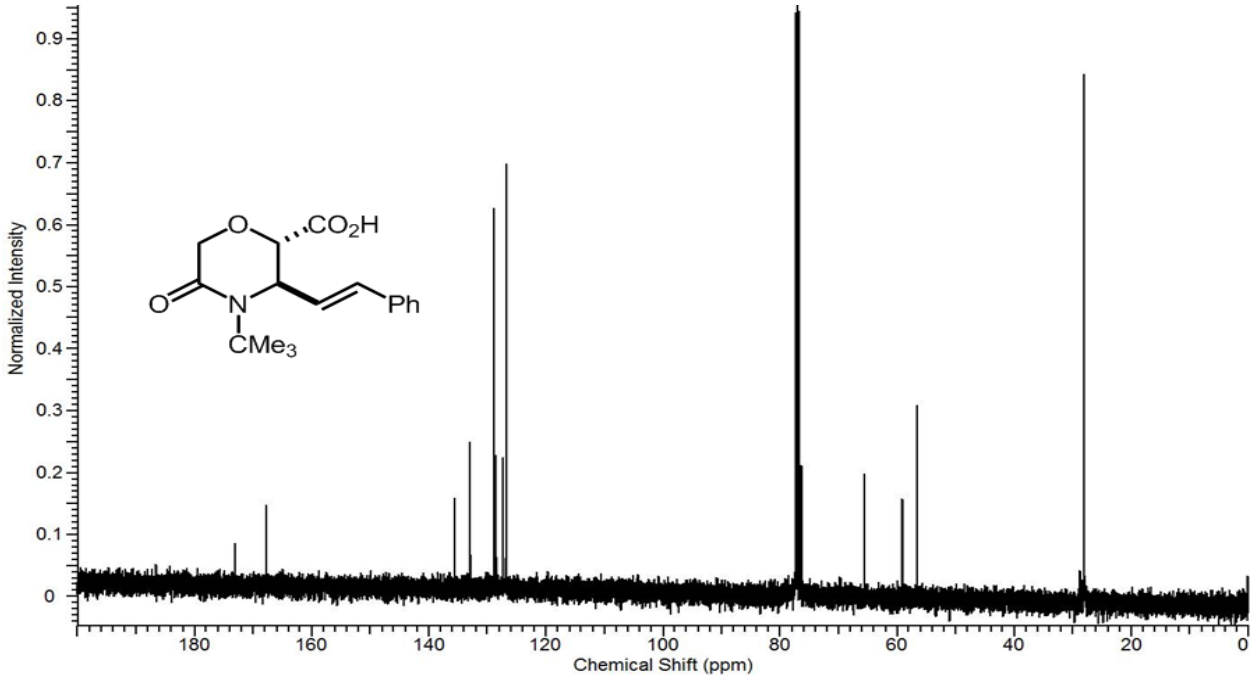
Spectrum 1-63: ^{13}C NMR spectrum of **5m2 major and minor.**



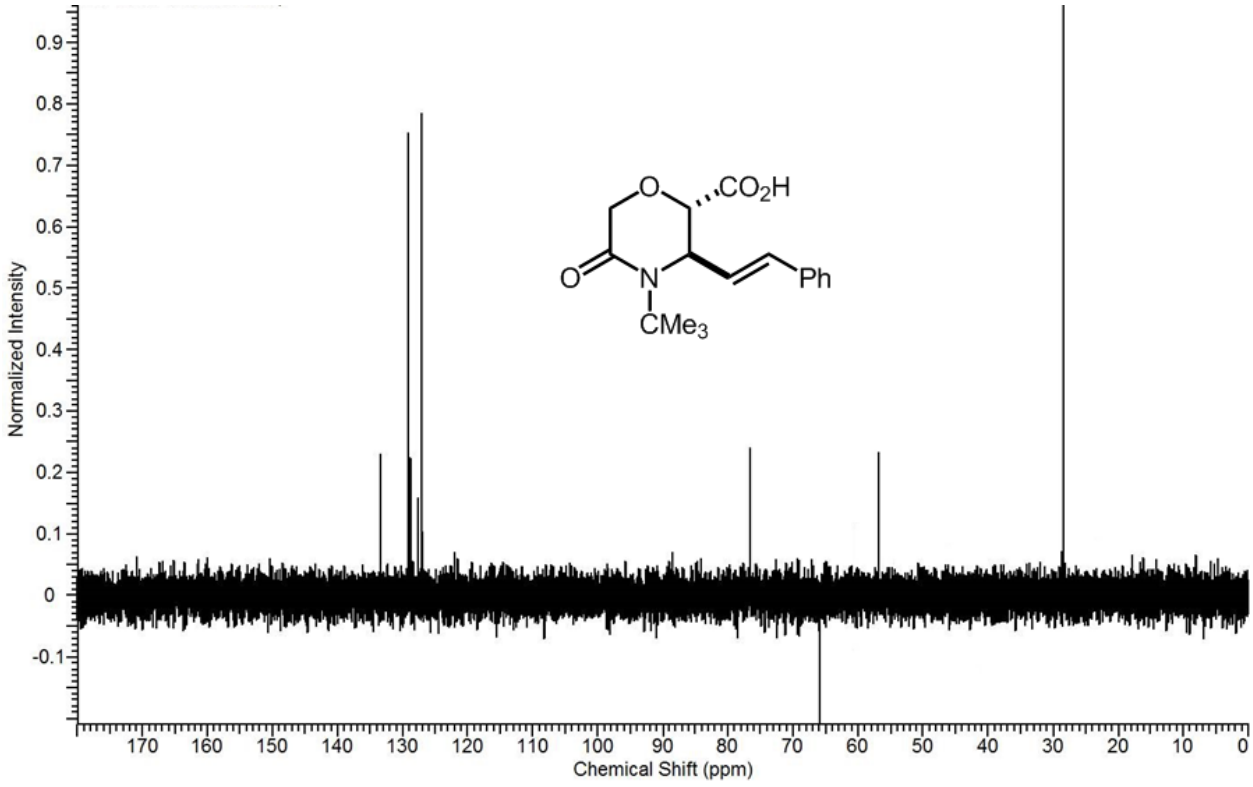
Spectrum 1-64: DEPT-135 NMR spectrum of **5m2 major and minor.**



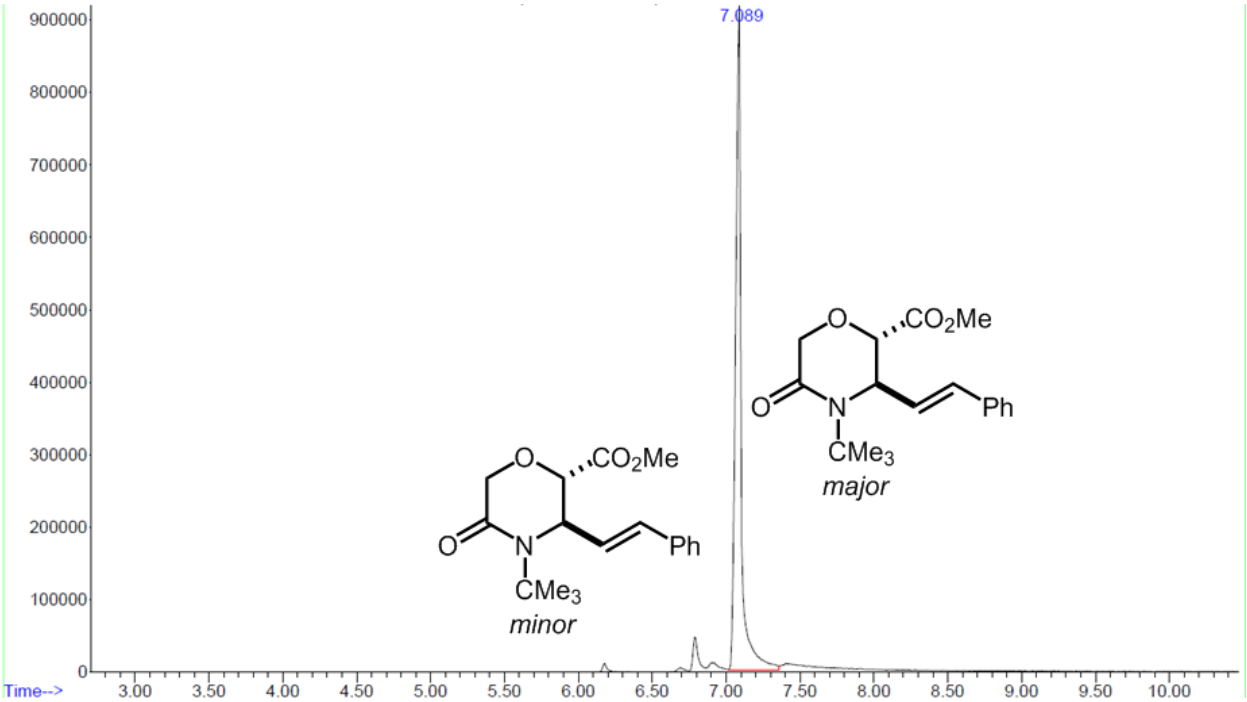
Spectrum 1-65: ^{1}H NMR spectrum of **5n1.**



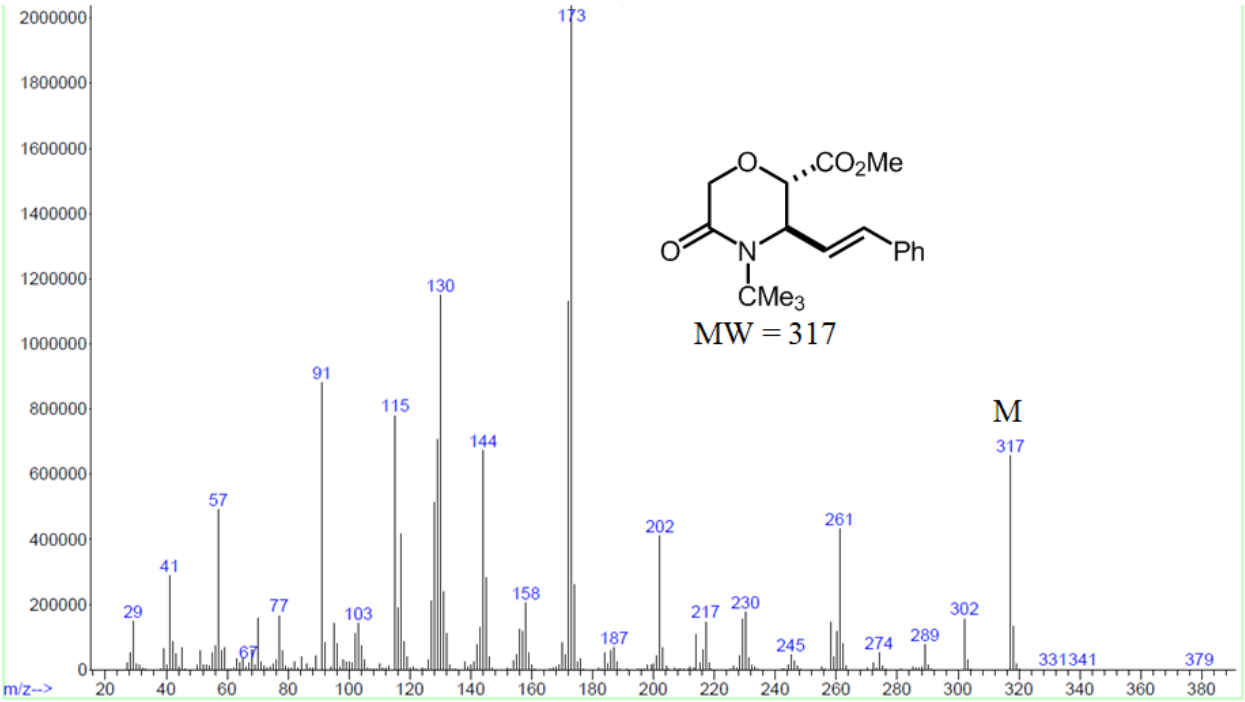
Spectrum 1-66: ^{13}C NMR spectrum of **5n1.**



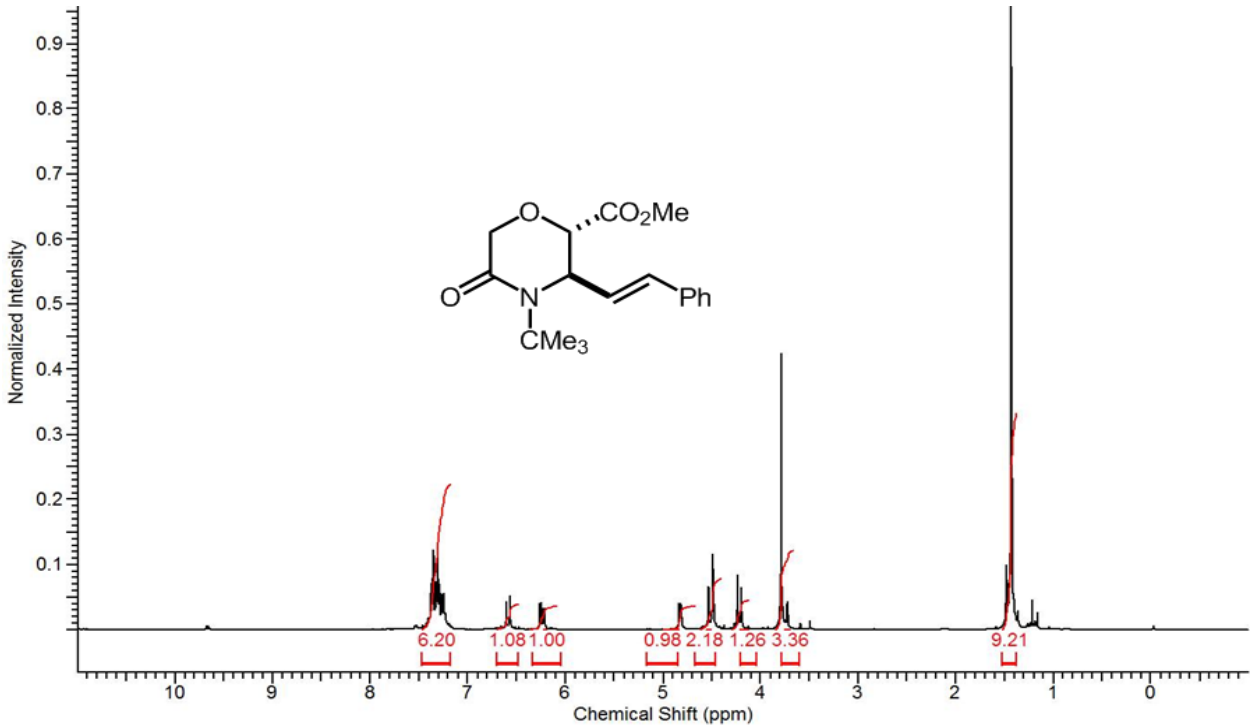
Spectrum 1-67: DEPT-135 NMR spectrum of **5n1.**



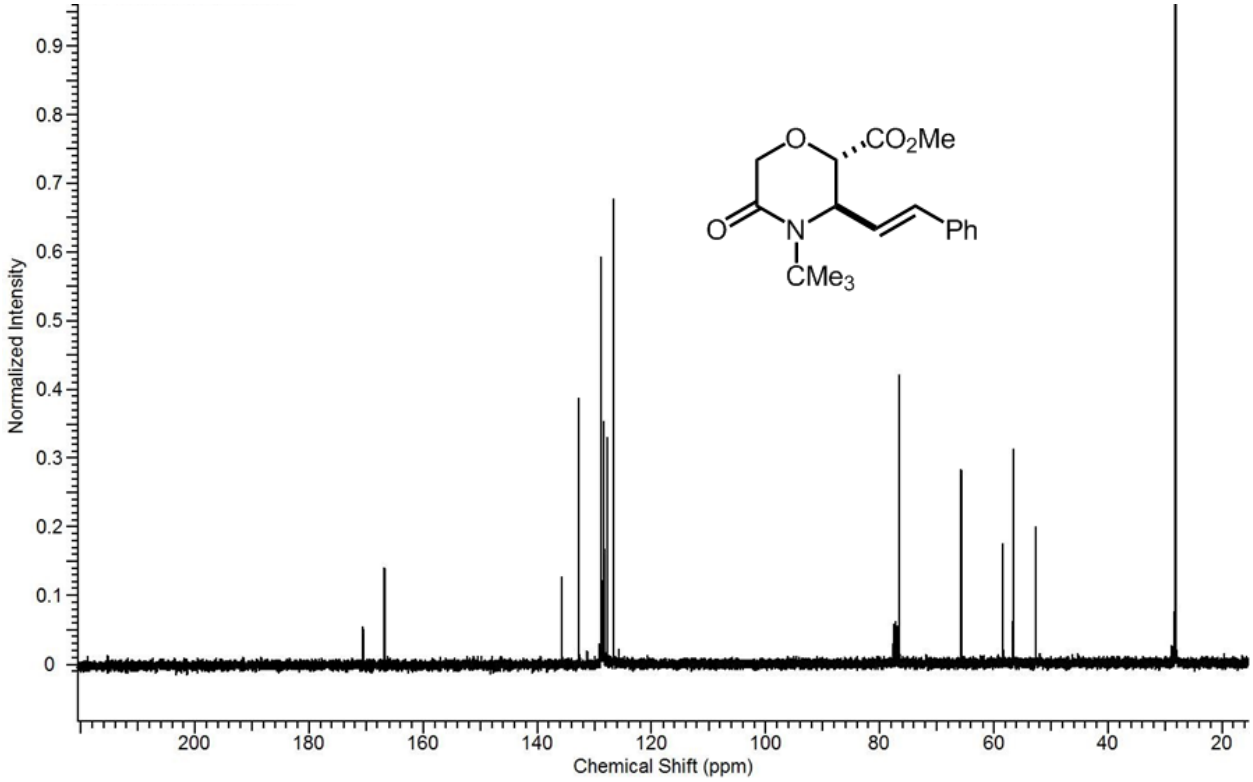
Spectrum 1-68: GC spectrum of **5n2 major and minor.**



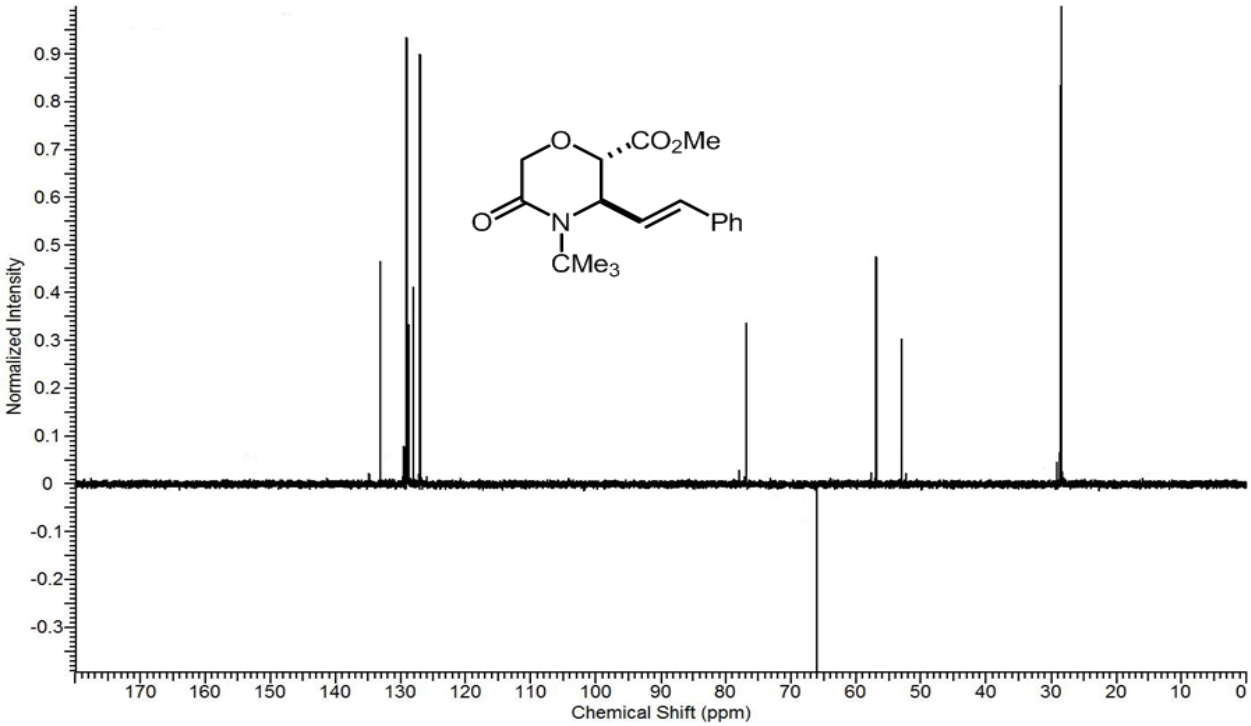
Spectrum 1-69: MS spectrum of **5n2 major.**



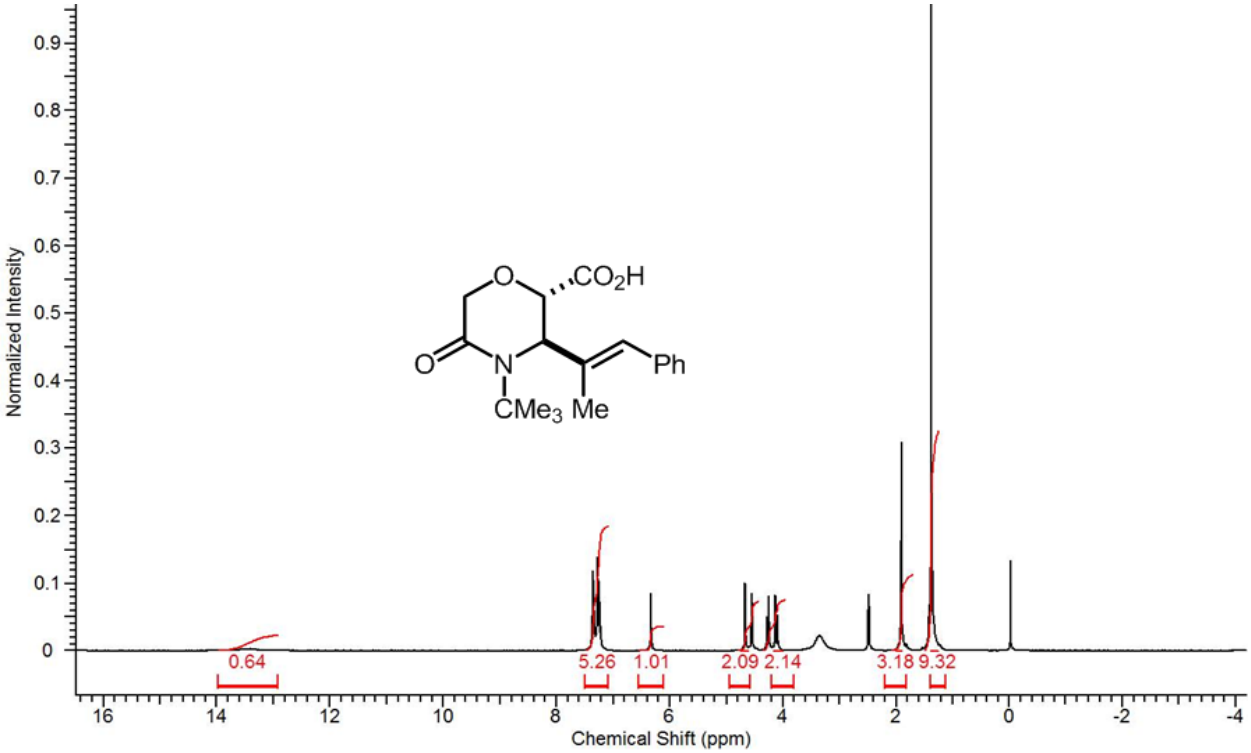
Spectrum 1-70: ^{1}H NMR spectrum of **5n2 major.**



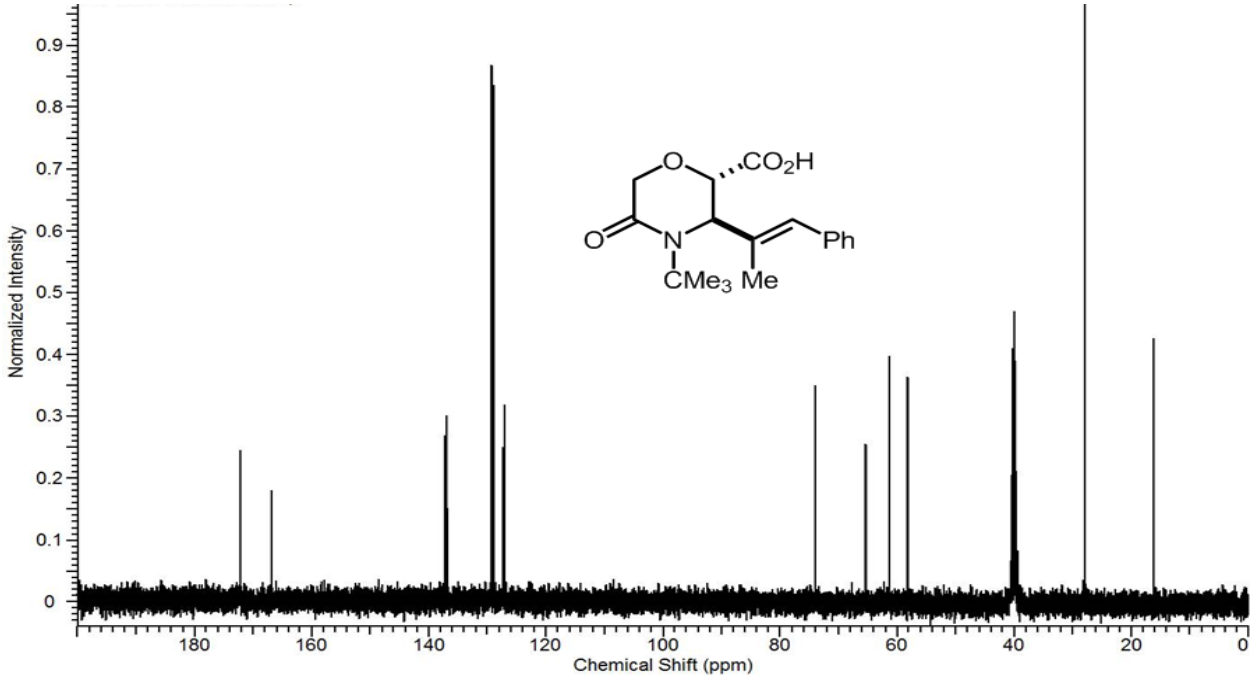
Spectrum 1-71: ^{13}C NMR spectrum of **5n2 major.**



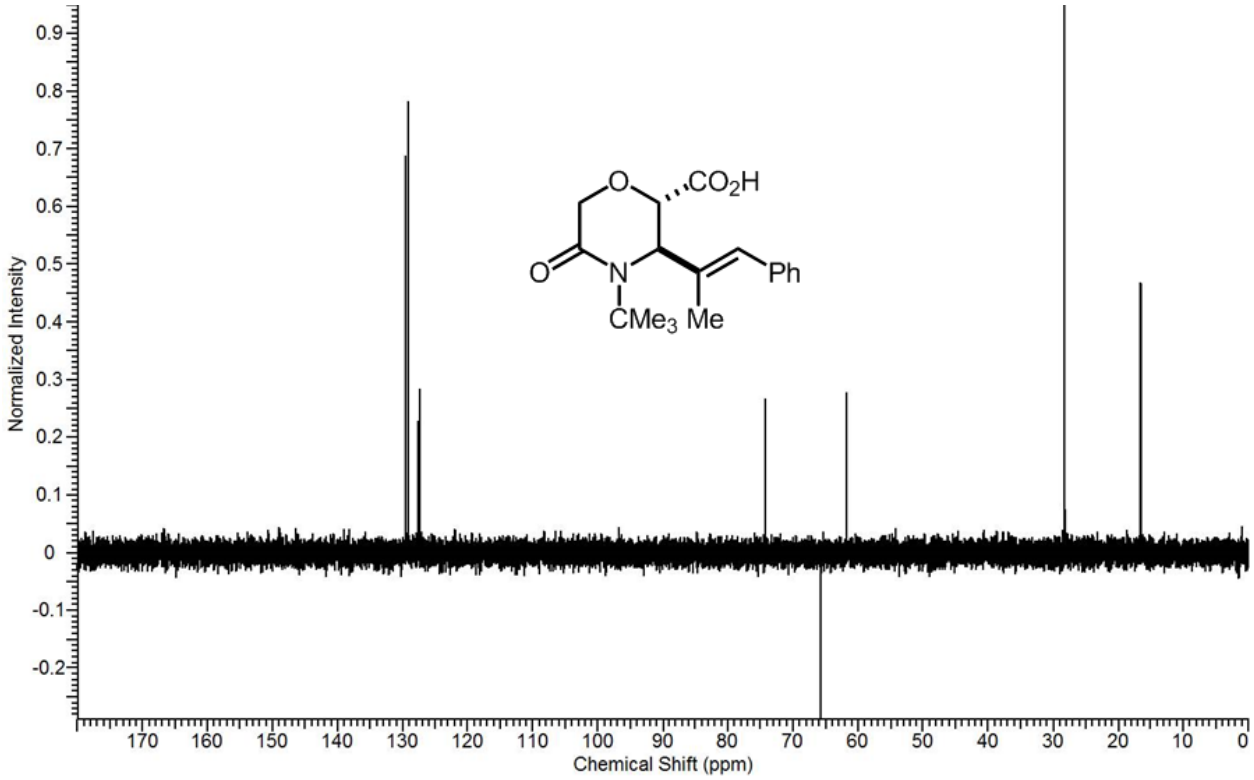
Spectrum 1-72: DEPT-135 NMR spectrum of **5n2 major.**



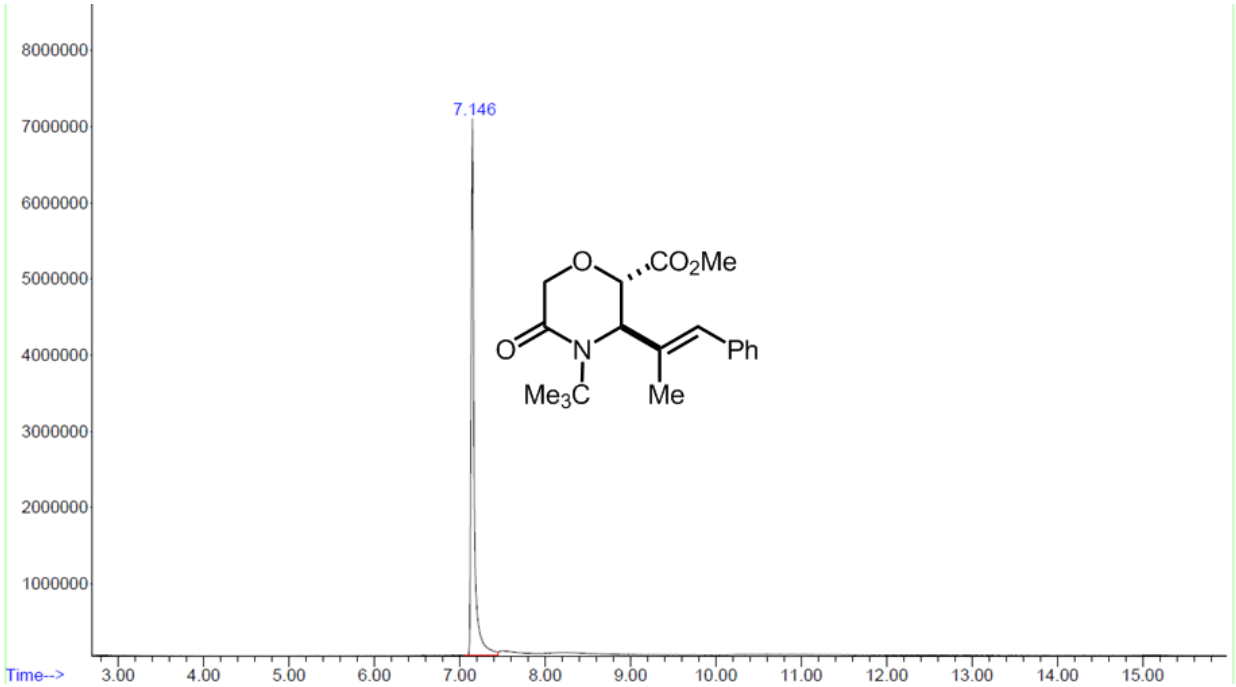
Spectrum 1-73: ^{1}H NMR spectrum of **5o1.**



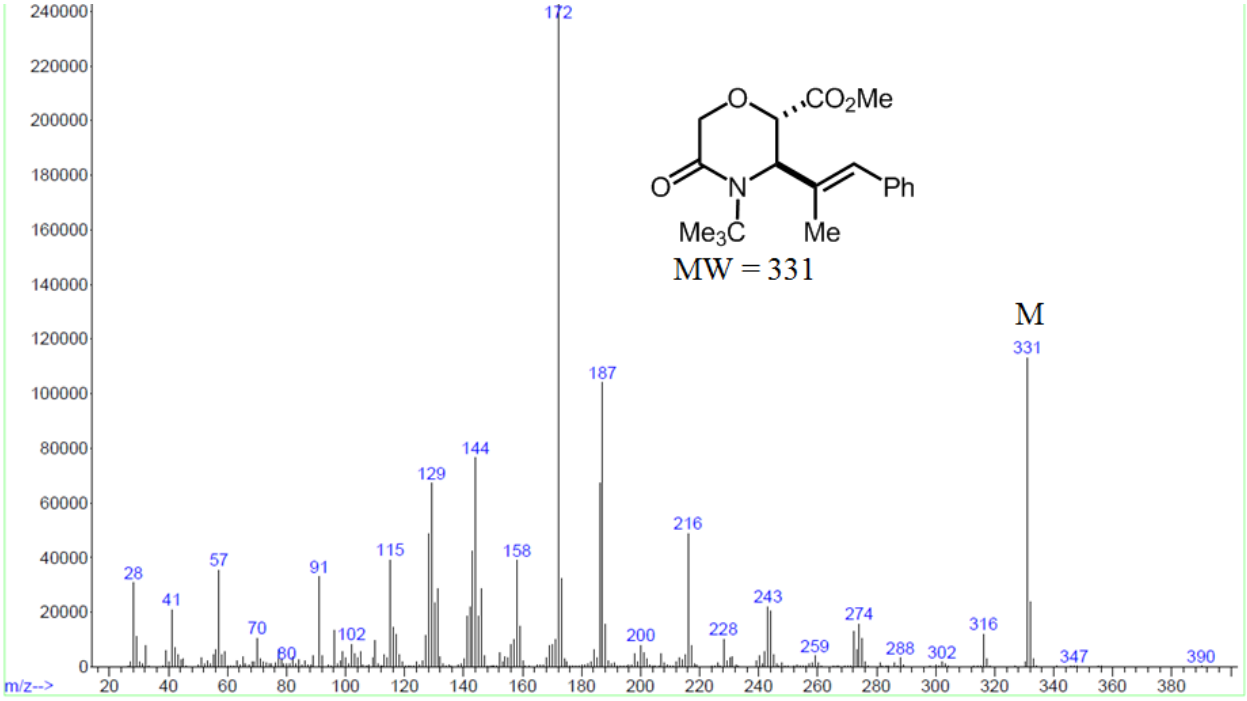
Spectrum 1-74: ^{13}C NMR spectrum of **5o1.**



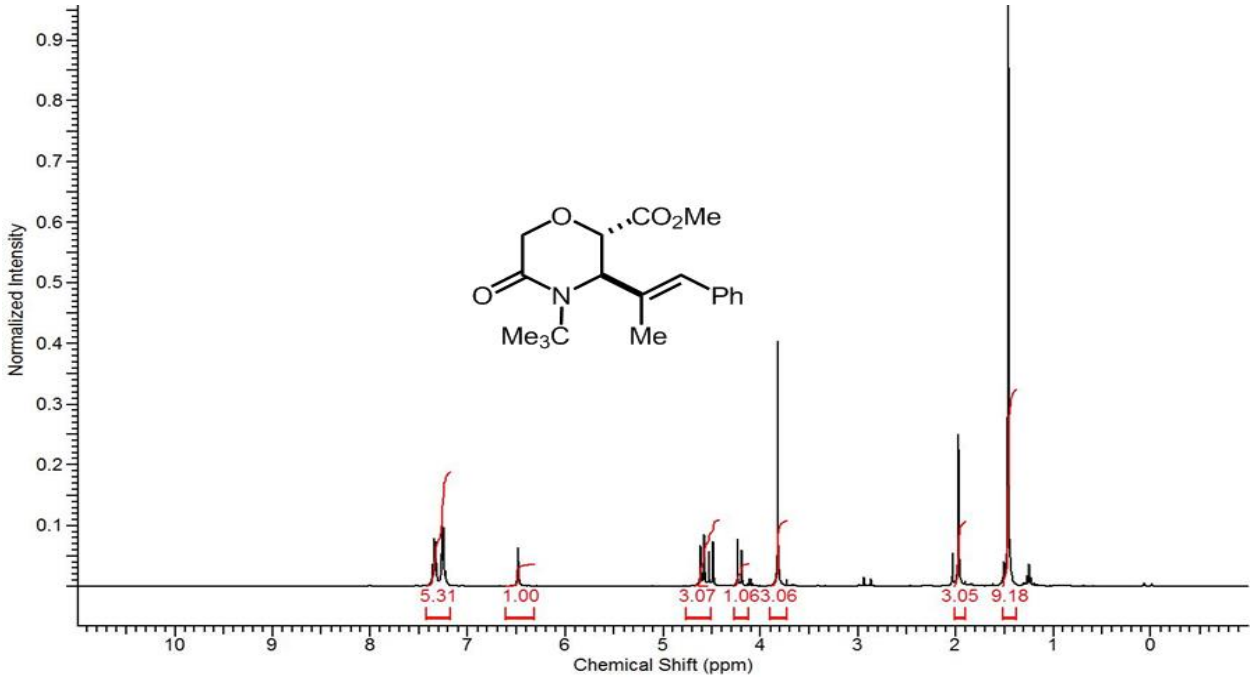
Spectrum 1-75: DEPT-135 NMR spectrum of **5o1.**



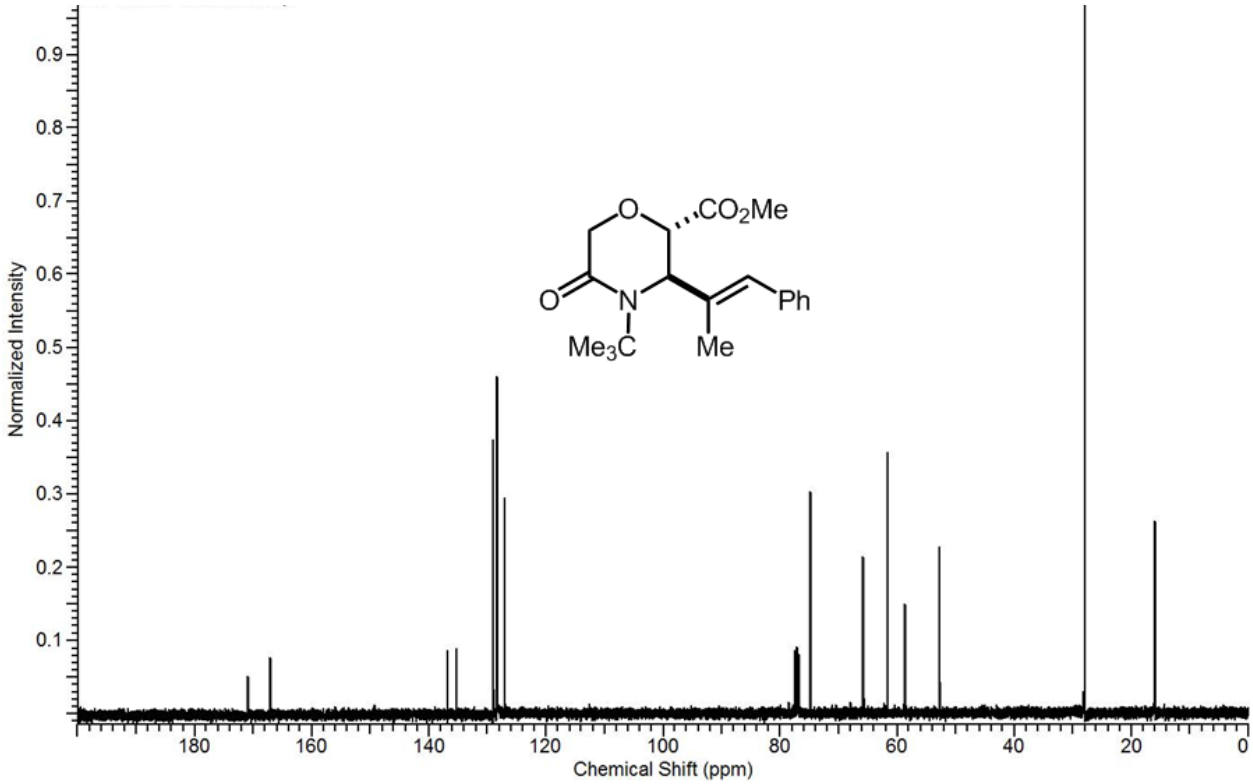
Spectrum 1-76: GC spectrum of **5o2.**



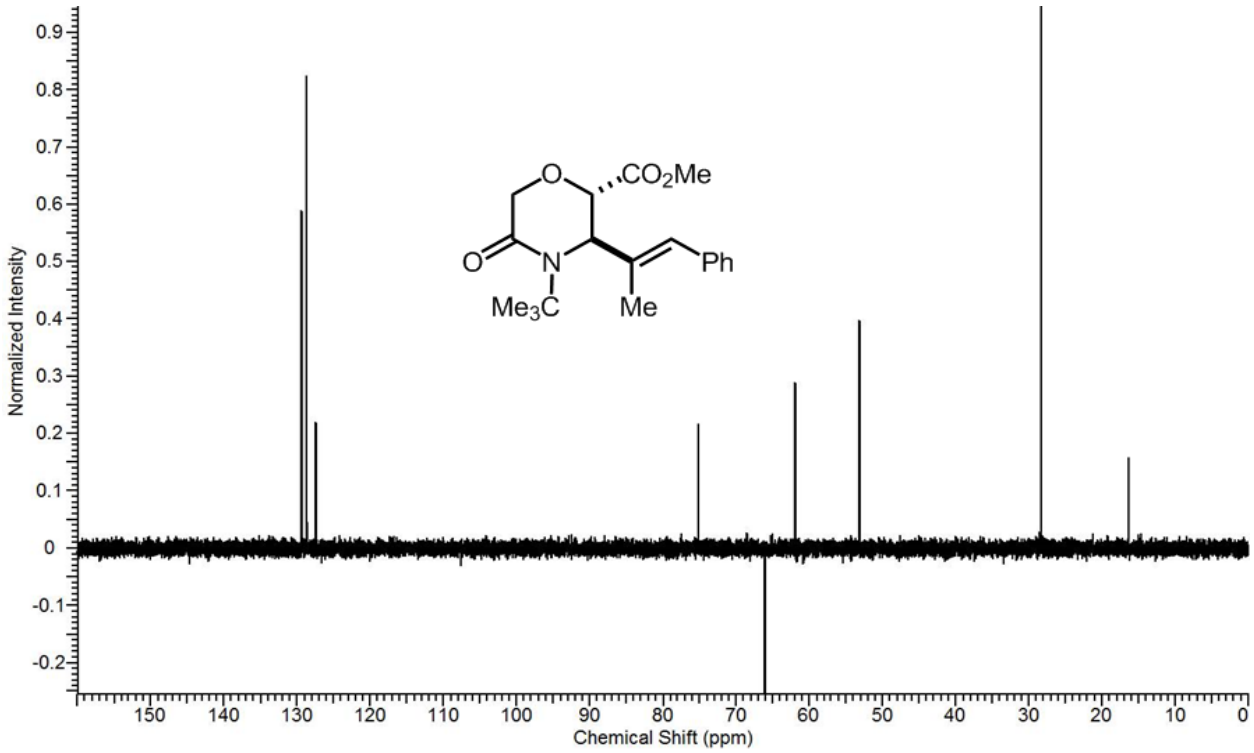
Spectrum 1-77: MS spectrum of **5o2.**



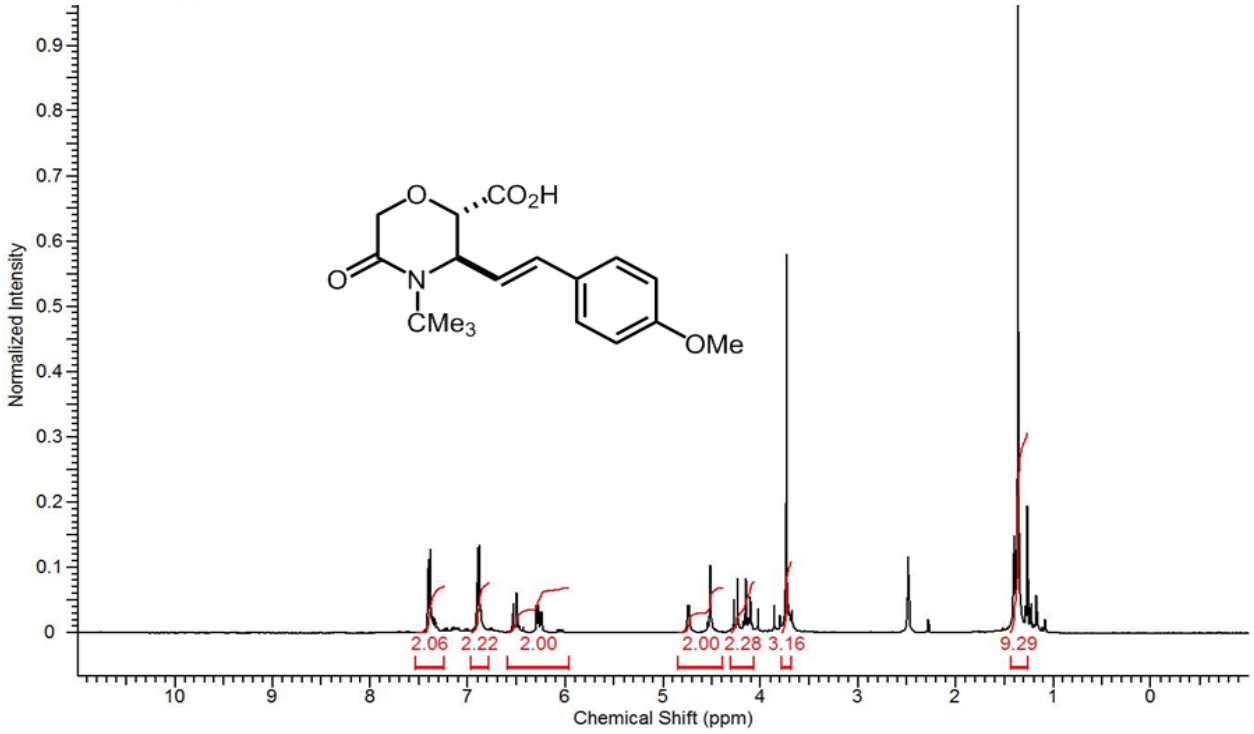
Spectrum 1-78: ^{1}H NMR spectrum of **5o2.**



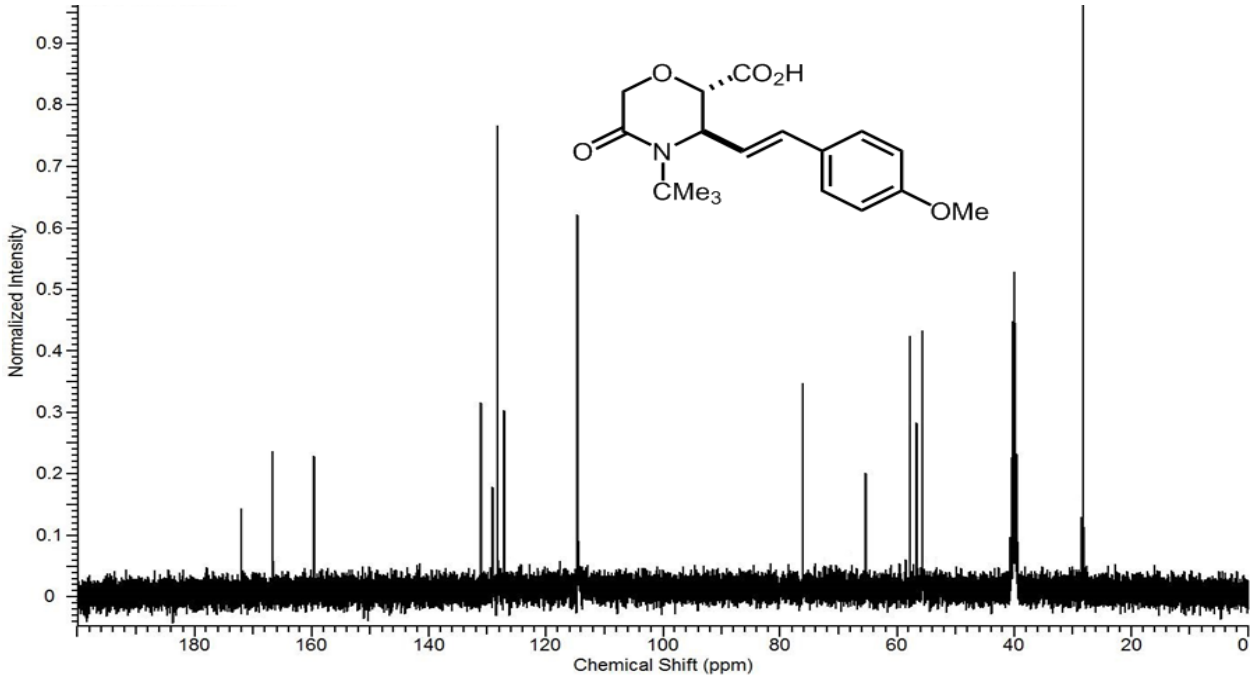
Spectrum 1-79: ^{13}C NMR spectrum of **5o2.**



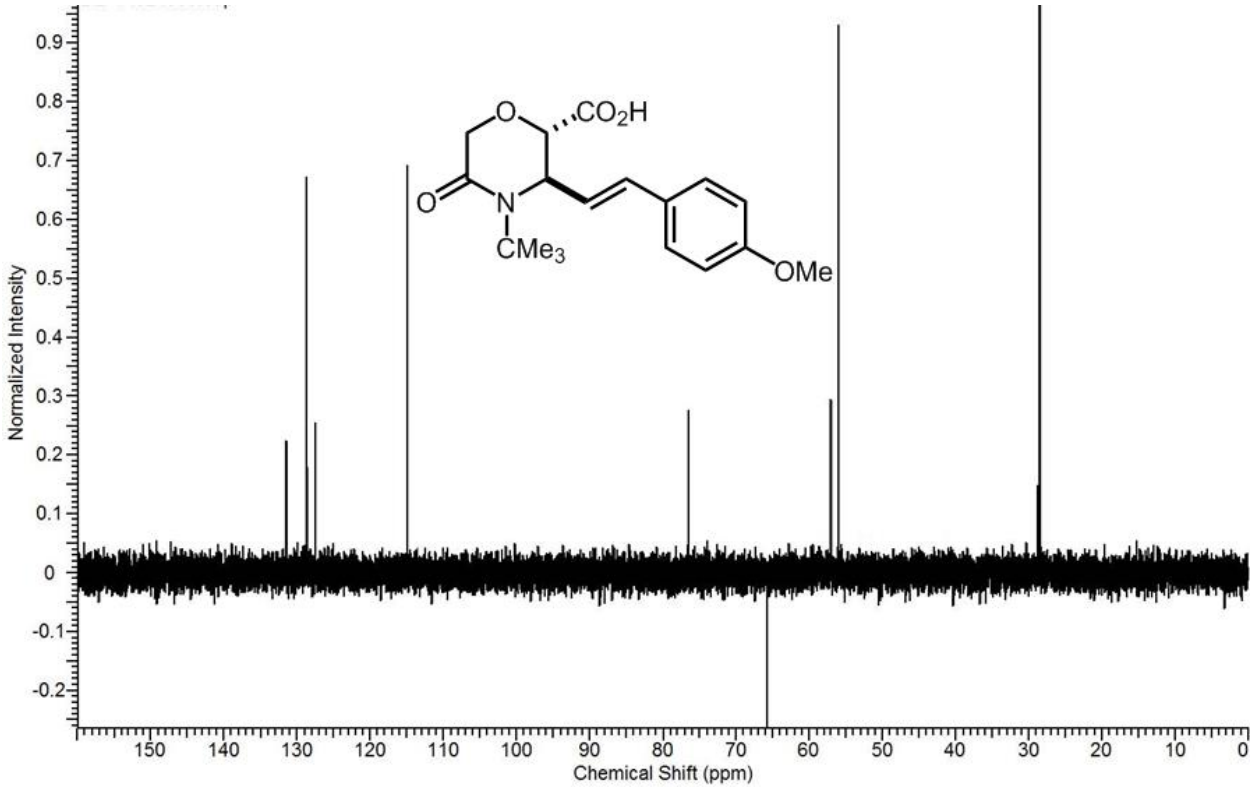
Spectrum 1-80: DEPT-135 NMR spectrum of **5o2.**



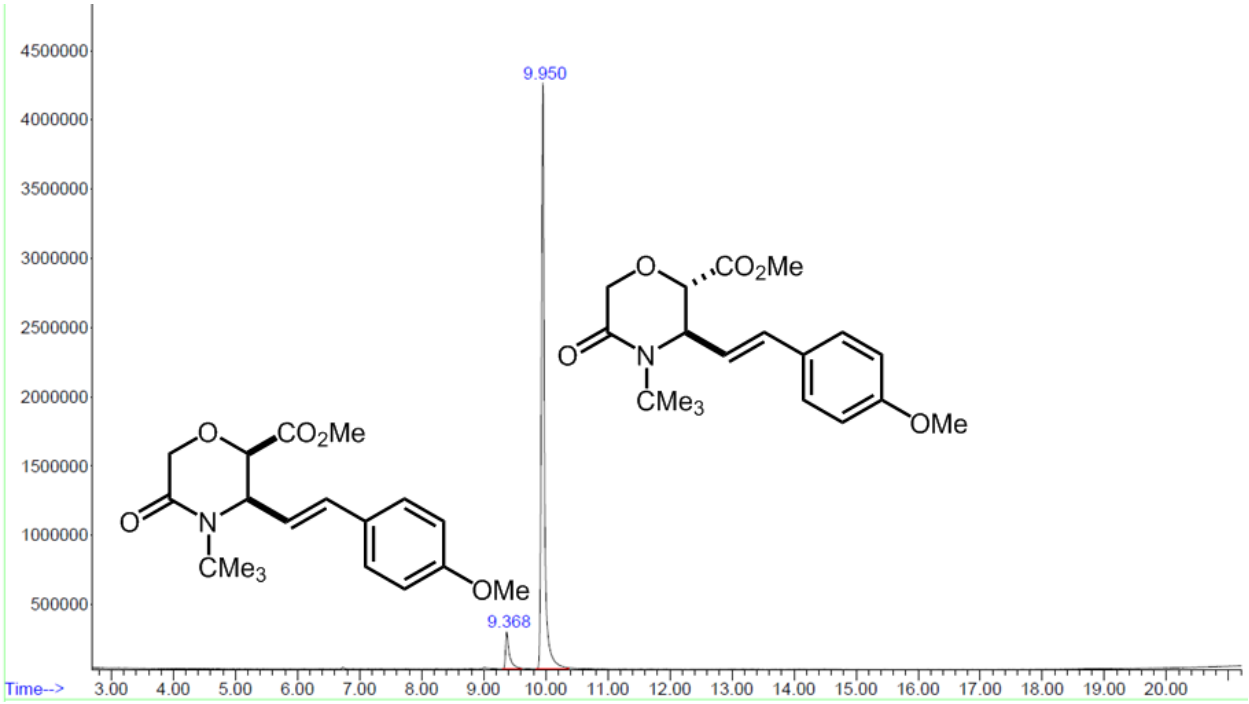
Spectrum 1-81: ^{1}H NMR spectrum of **5p1.**



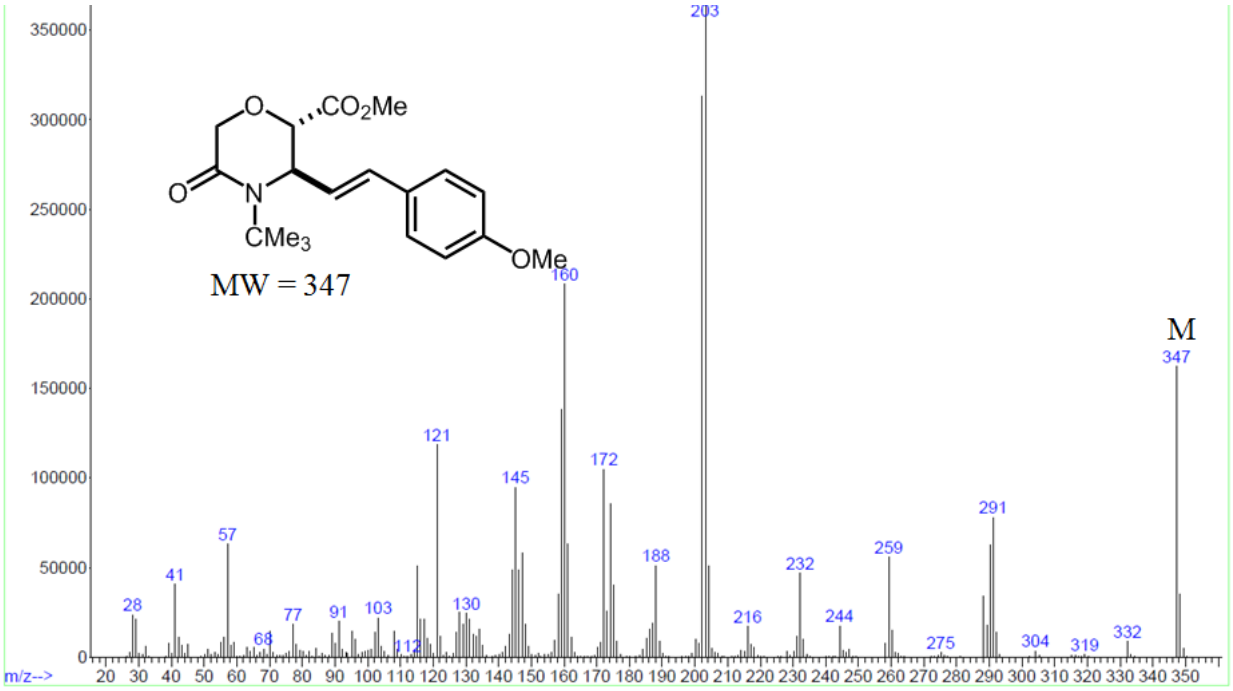
Spectrum 1-82: ^{13}C NMR spectrum of **5p1.**



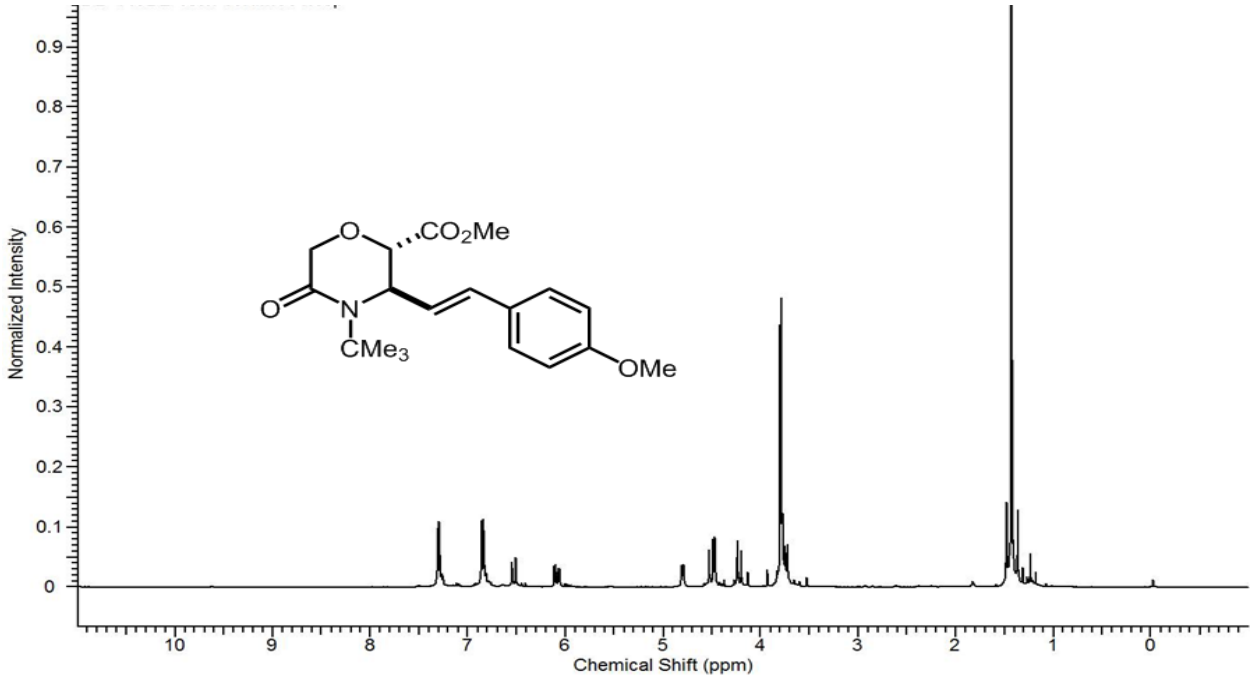
Spectrum 1-83: DEPT-135 NMR spectrum of **5p1.**



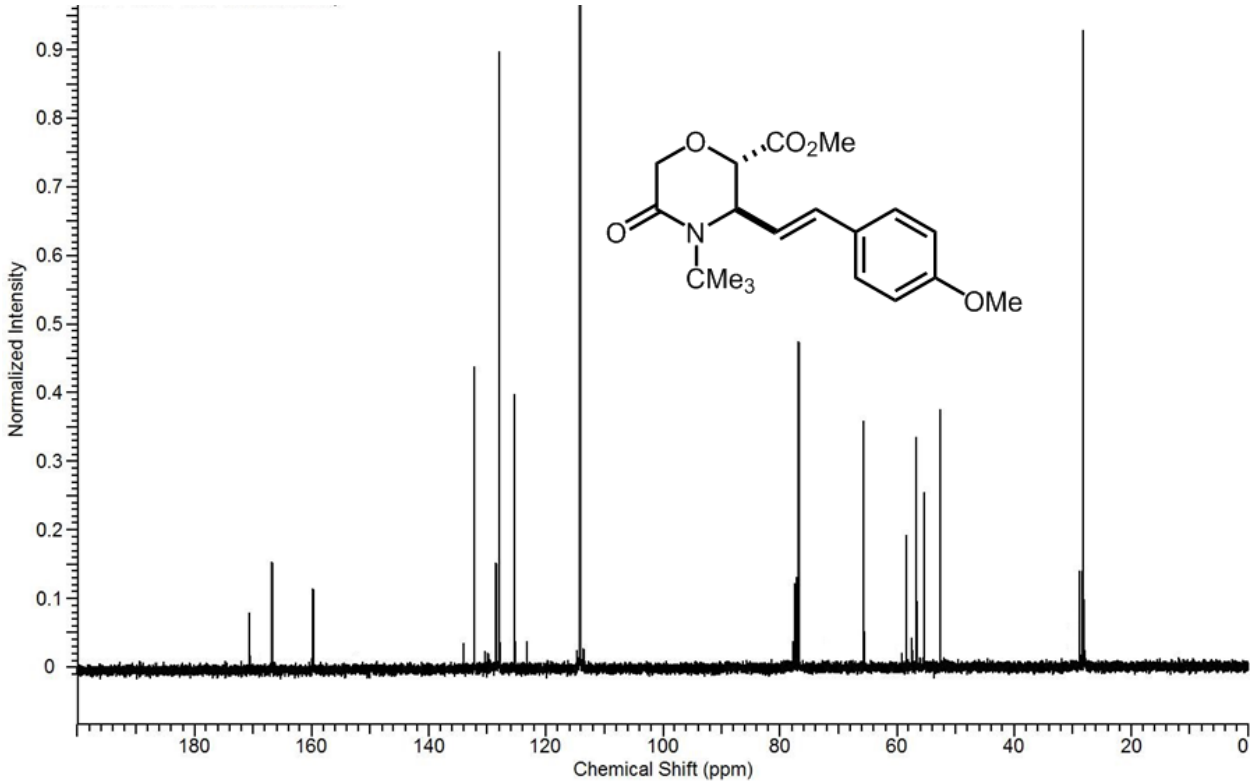
Spectrum 1-84: GC spectrum of **5p2 major and minor.**



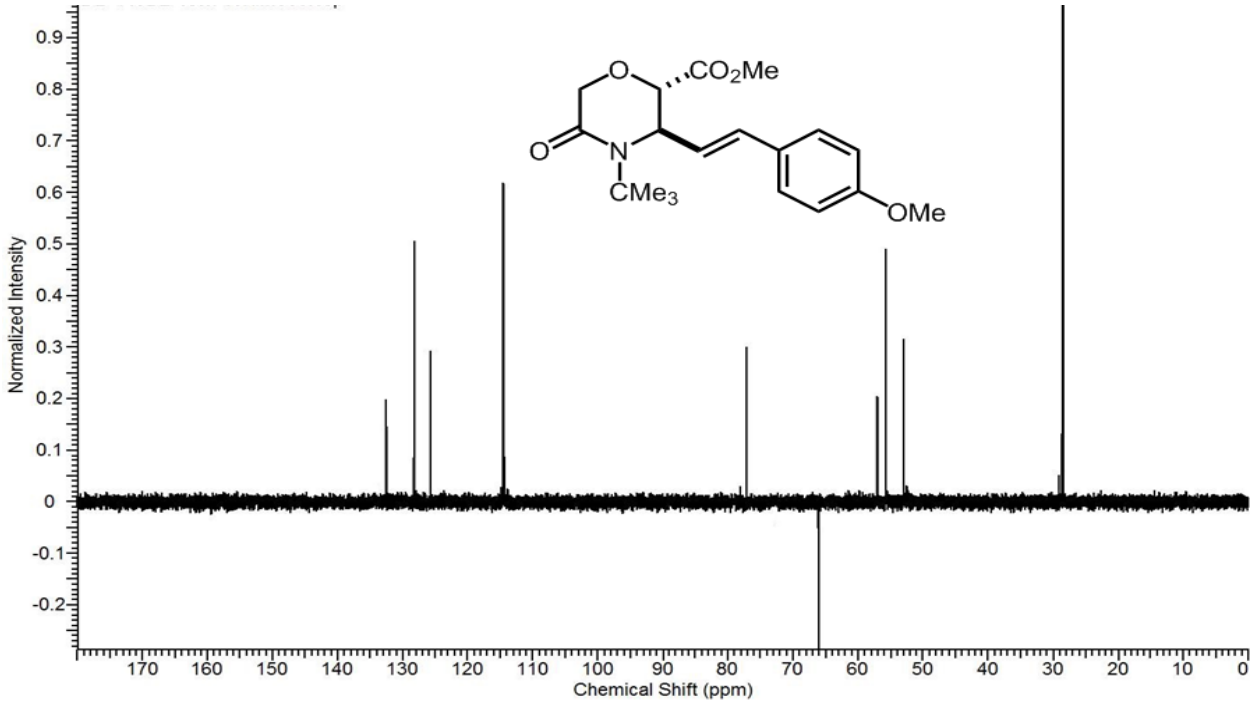
Spectrum 1-85: MS spectrum of **5p2.**



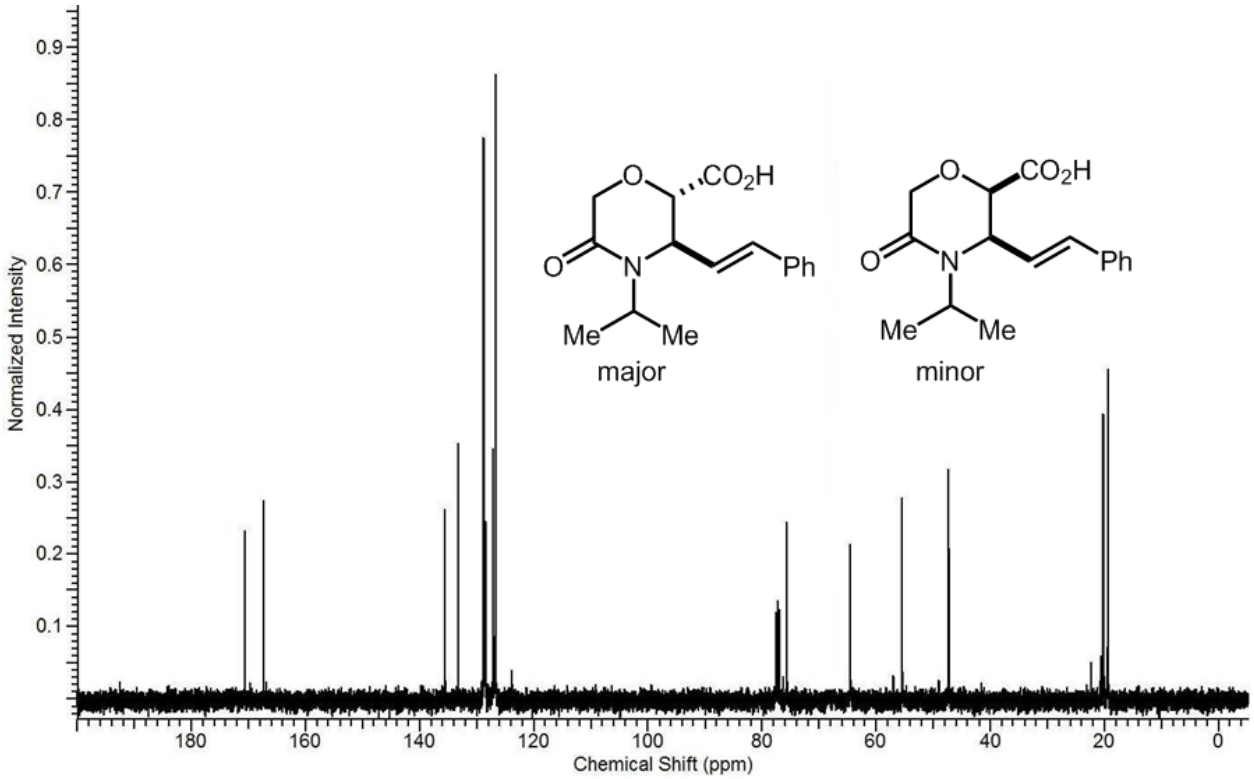
Spectrum 1-86: ^{1}H NMR spectrum of **5p2.**



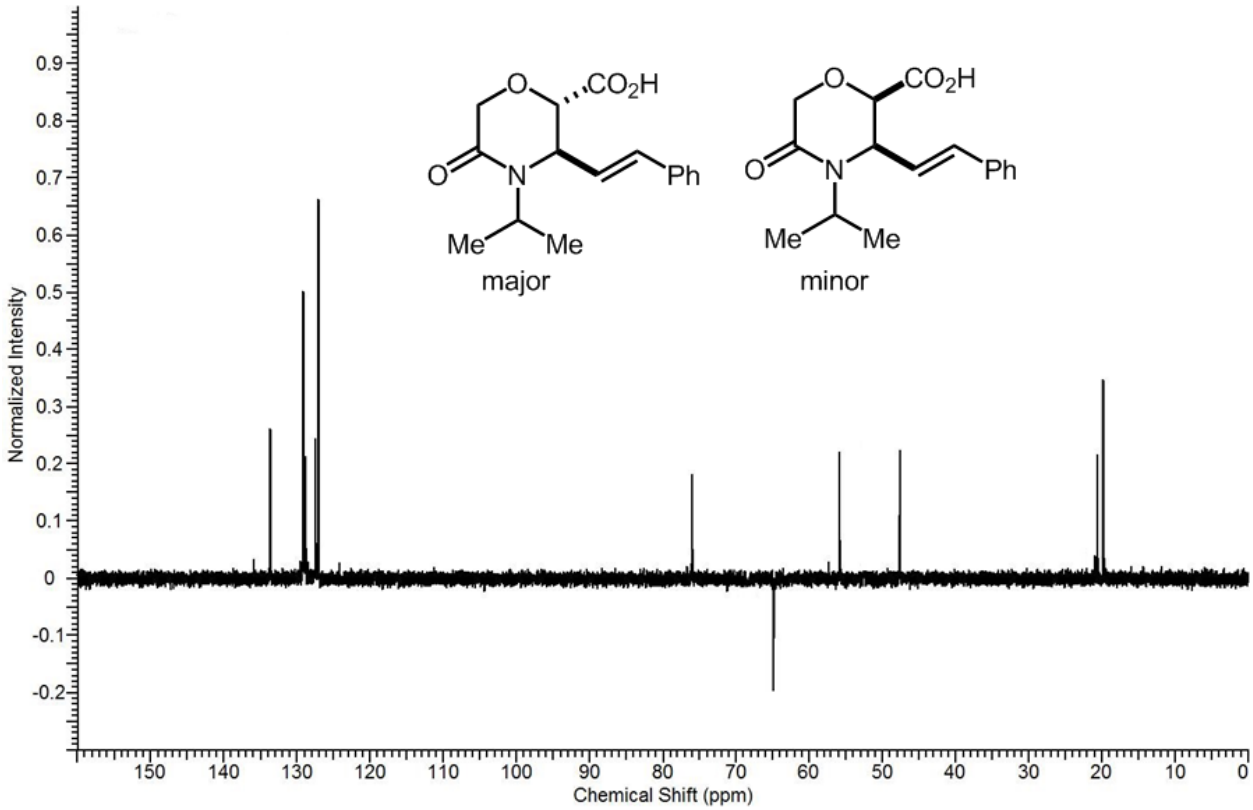
Spectrum 1-87: ^{13}C NMR spectrum of **5p2.**



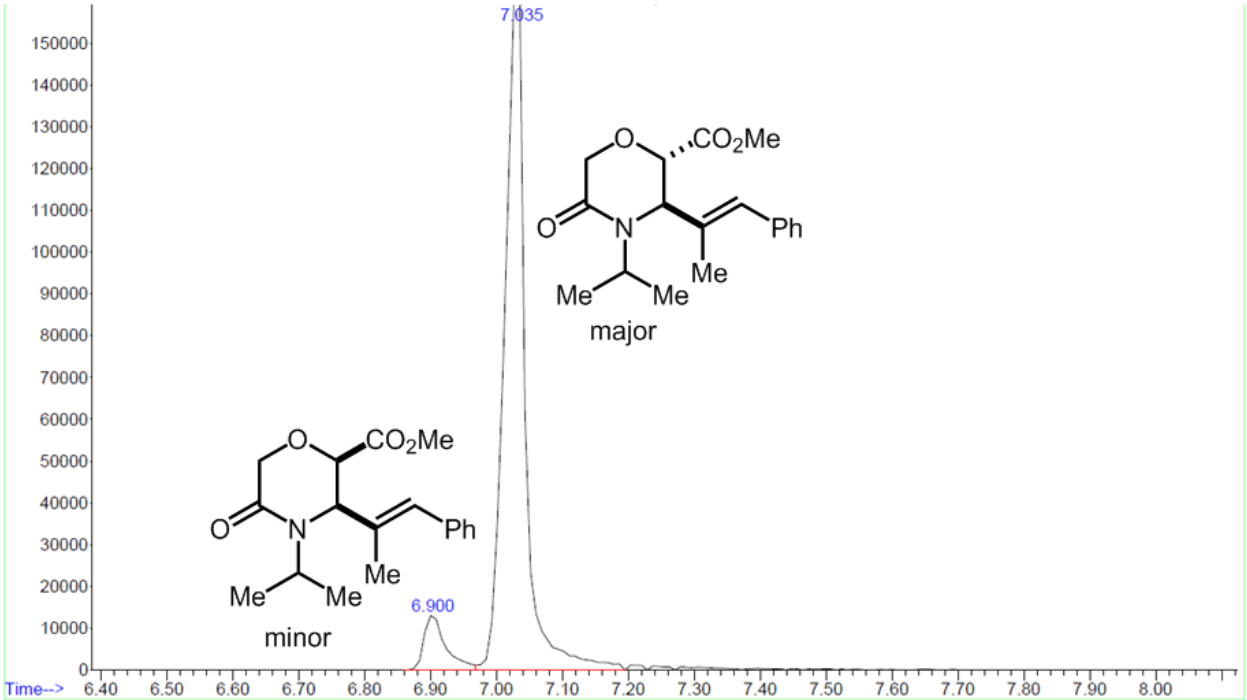
Spectrum 1-88: DEPT-135 NMR spectrum of **5p2.**



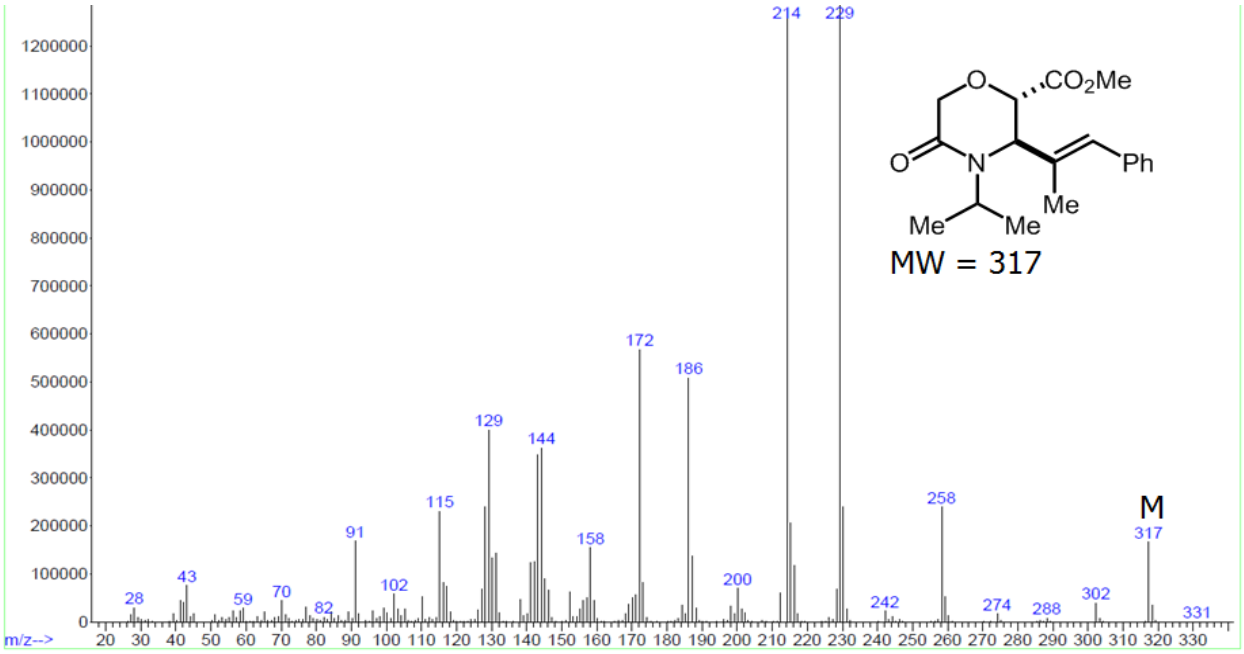
Spectrum 1-89: ^{13}C NMR spectrum of **5q1 major and minor.**



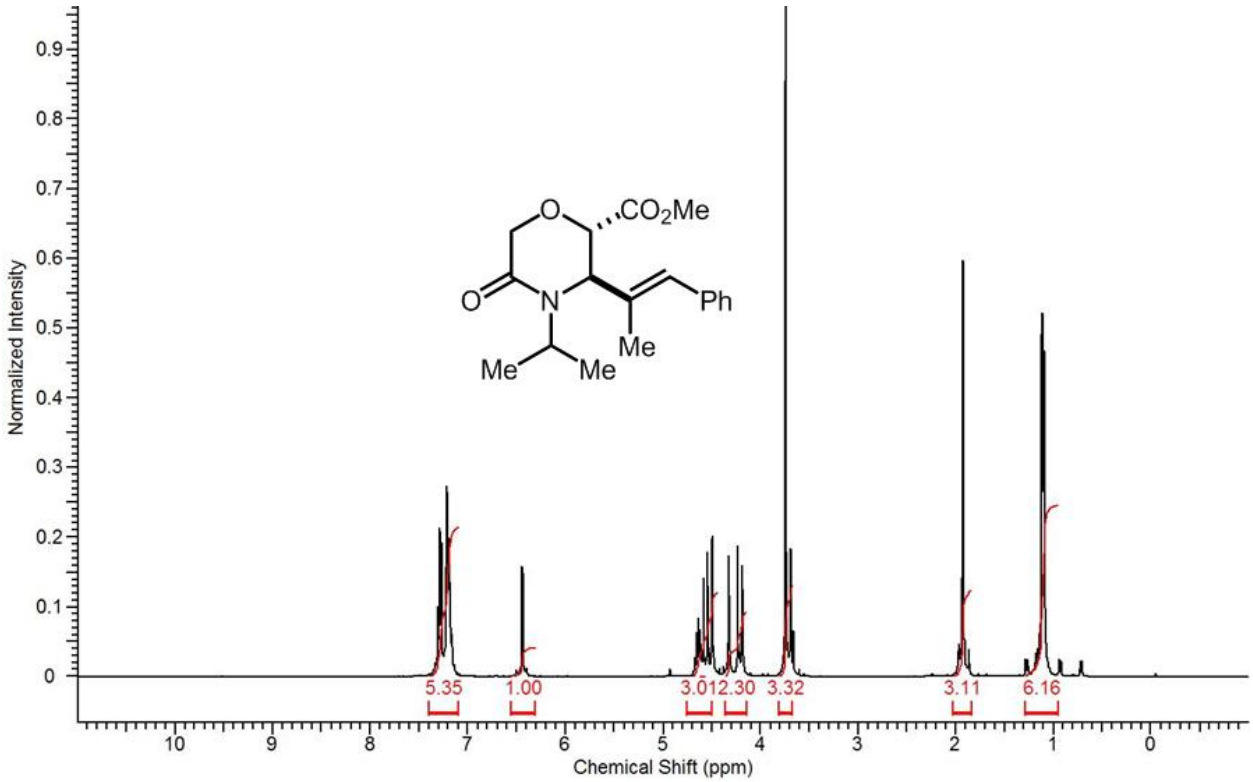
Spectrum 1-90: DEPT-135 NMR spectrum of **5q1 major and minor.**



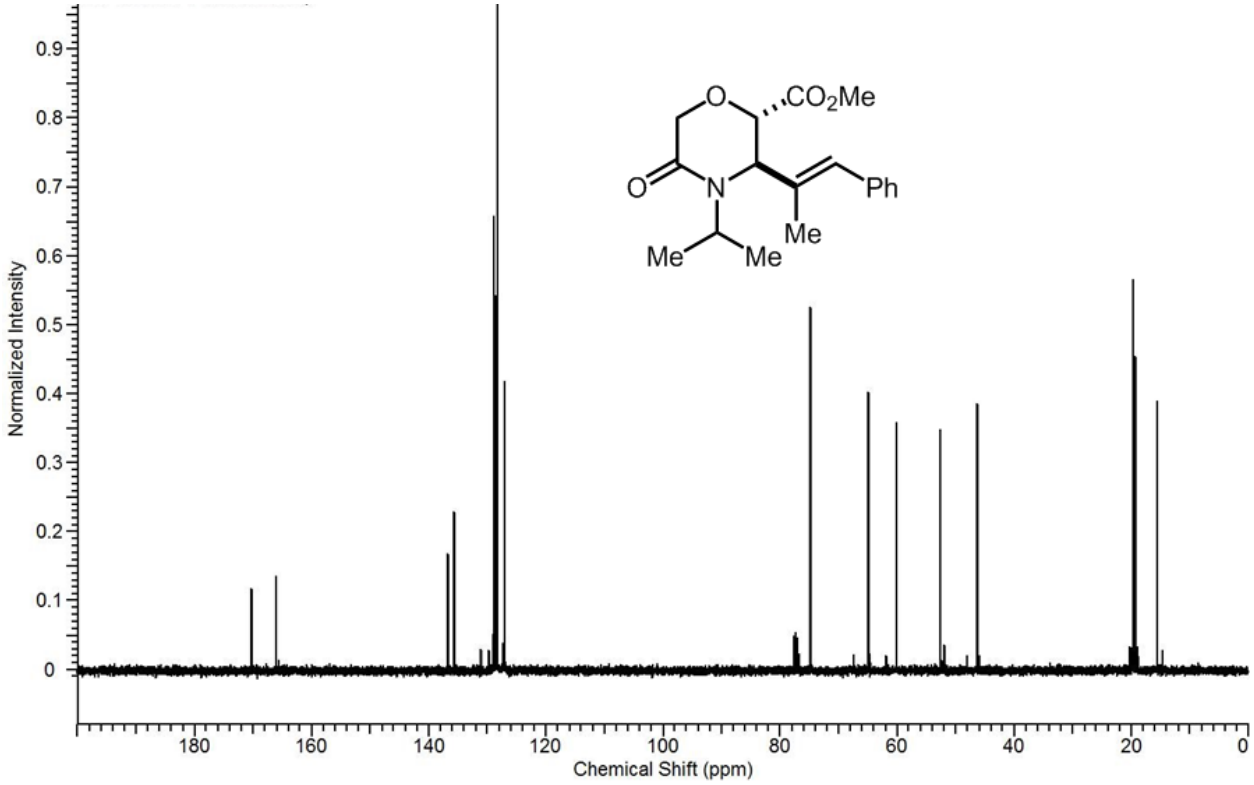
Spectrum 1-91: GC spectrum of **5r2 major and minor.**



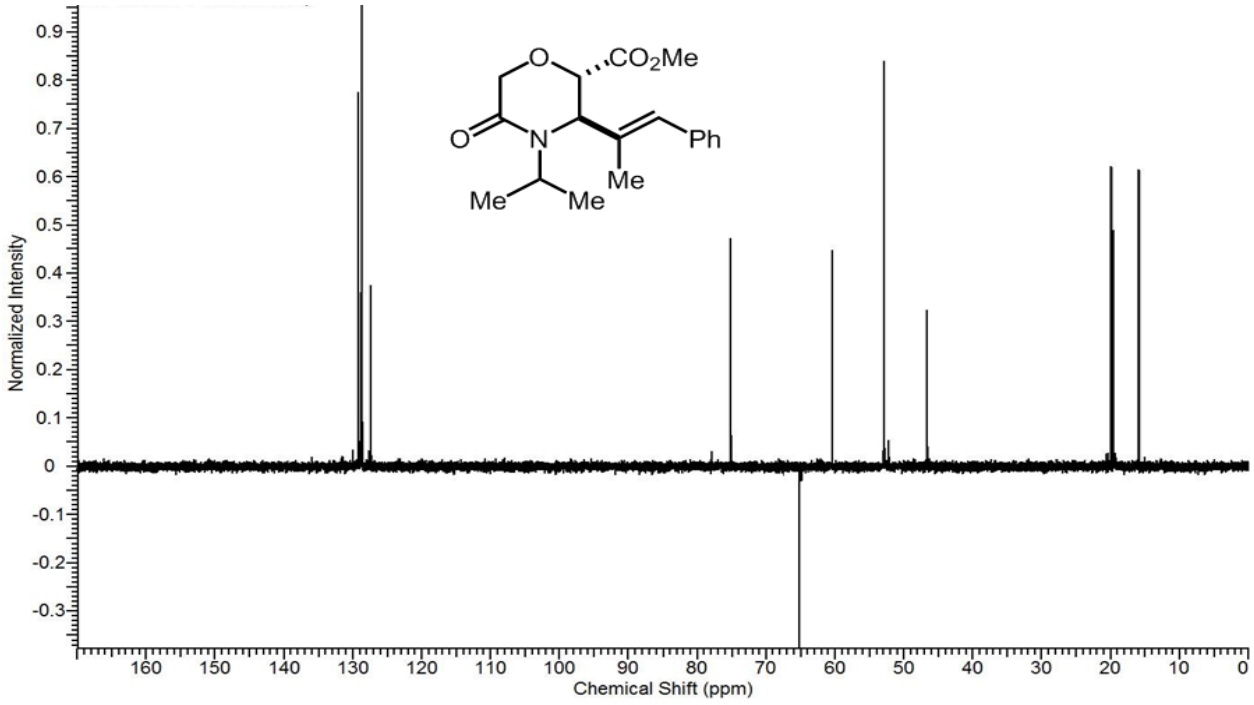
Spectrum 1-92: MS spectrum of **5r2 major.**



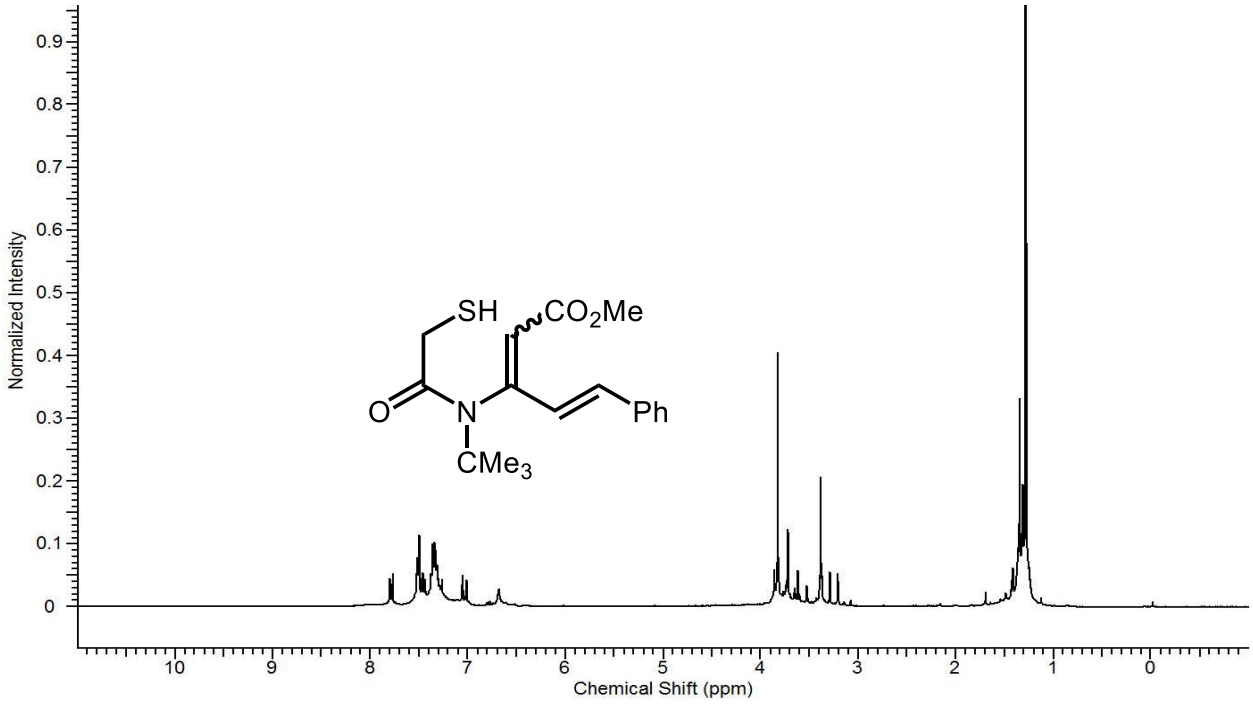
Spectrum 1-93: ^{1}H NMR spectrum of **5r2 major.**



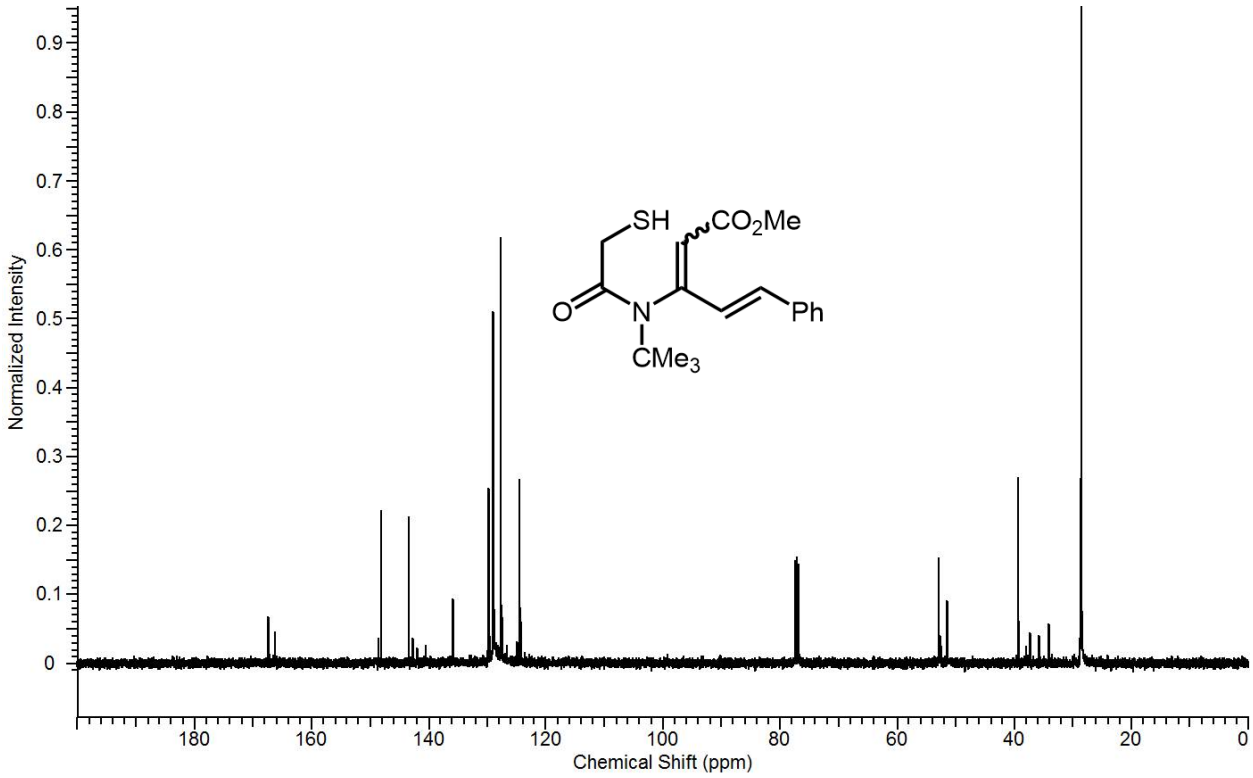
Spectrum 1-94: ^{13}C NMR spectrum of **5r2 major.**



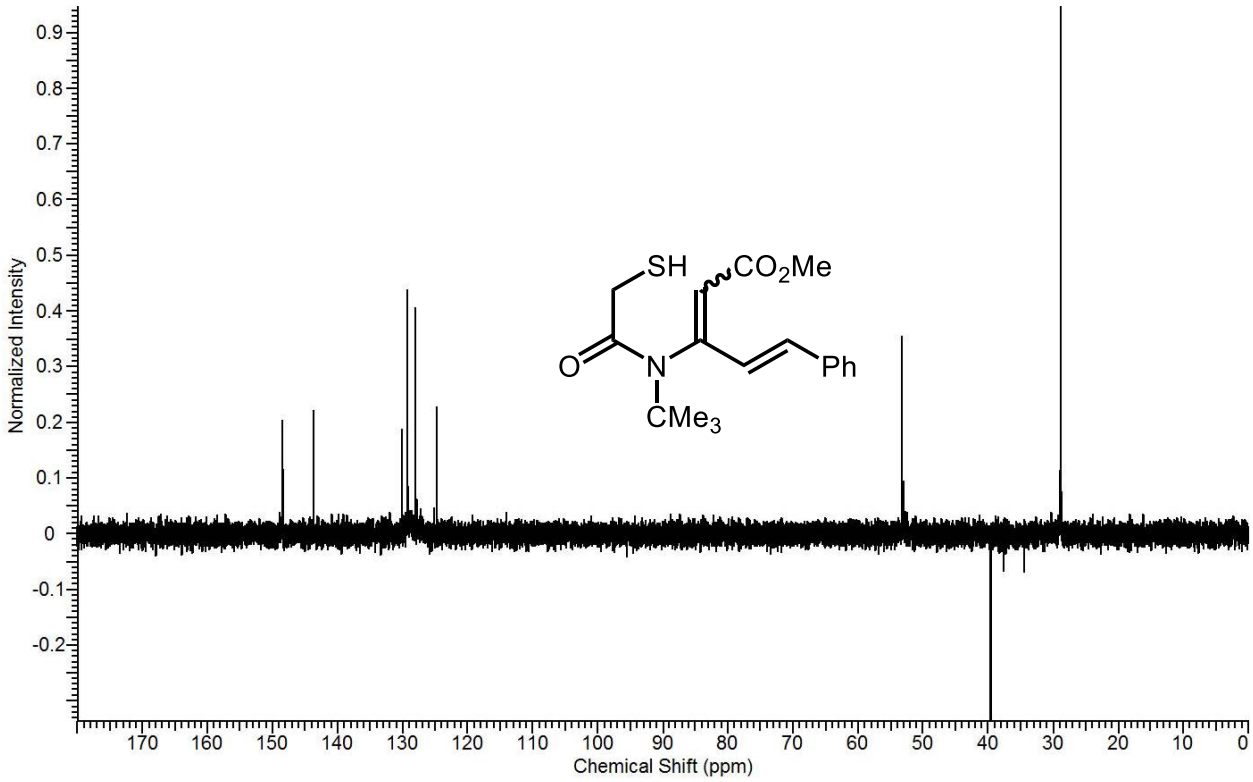
Spectrum 1-95: DEPT-135 NMR spectrum of **5r2 major.**



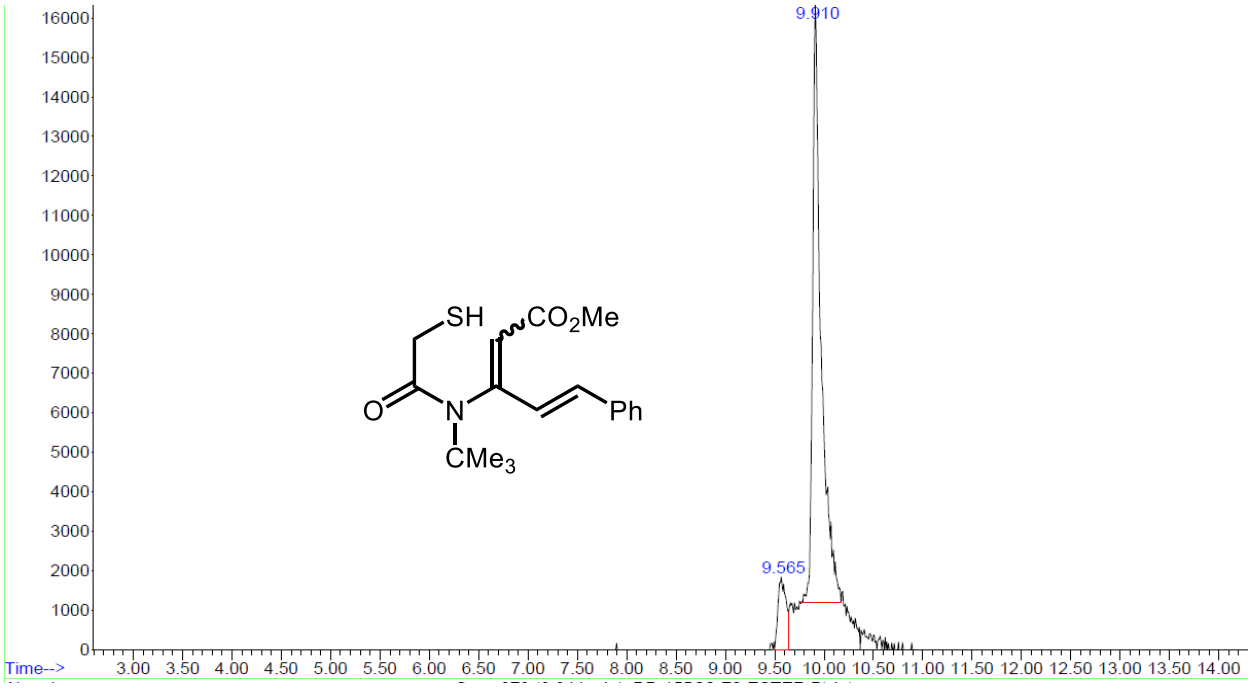
Spectrum 1-96: ^{1}H NMR spectrum of **6b2'.**



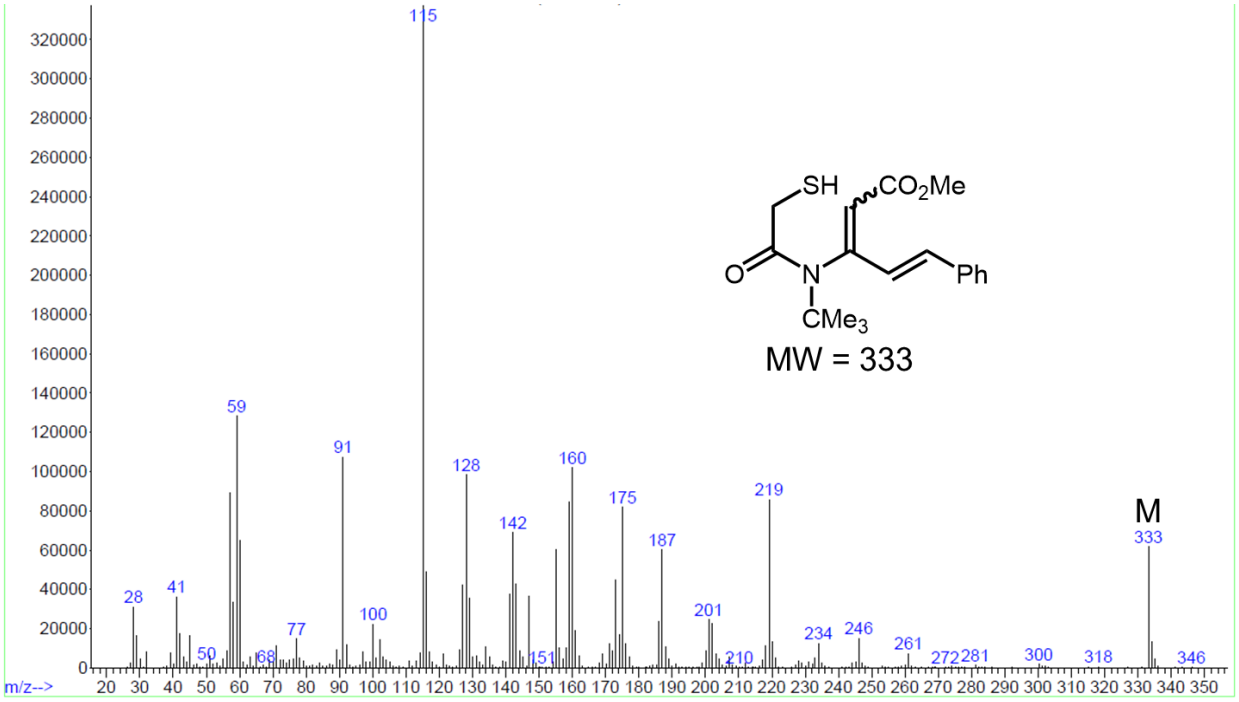
Spectrum 1-97: ^{13}C NMR spectrum of **6b2'.**



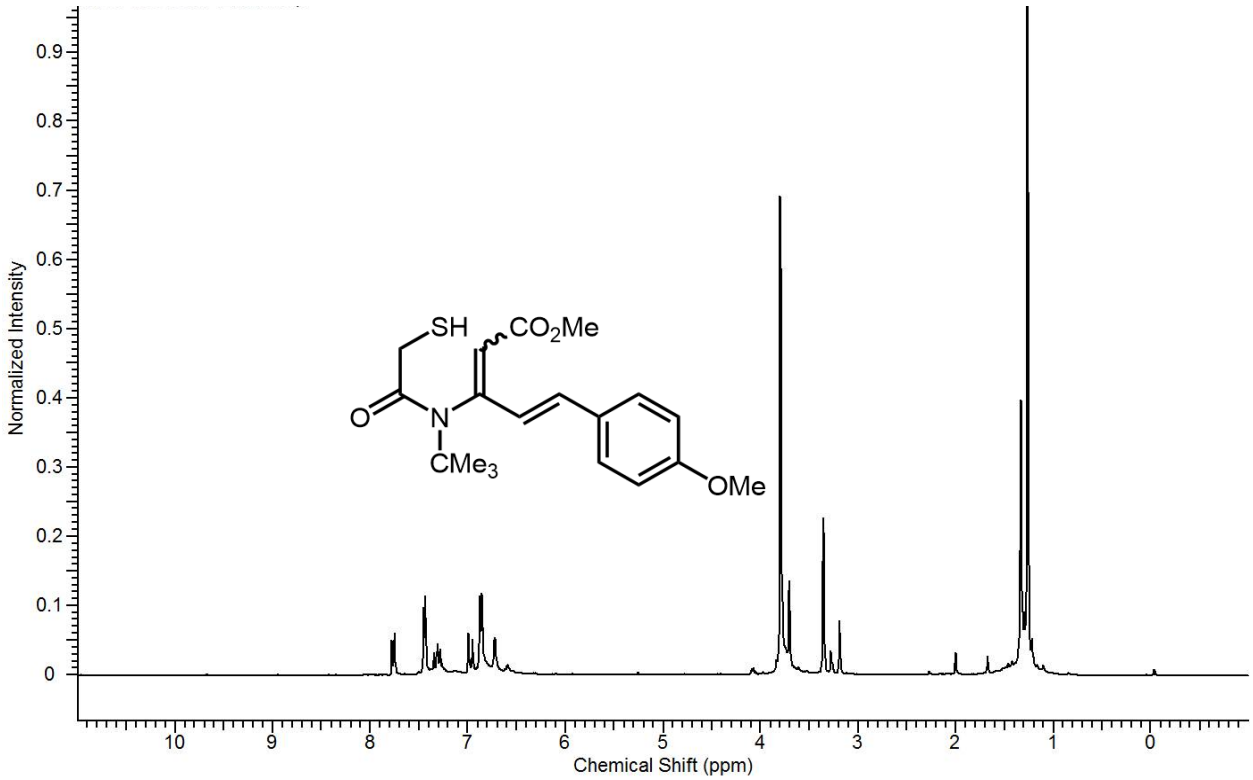
Spectrum 1-98: DEPT-135 NMR spectrum of **6b2'.**



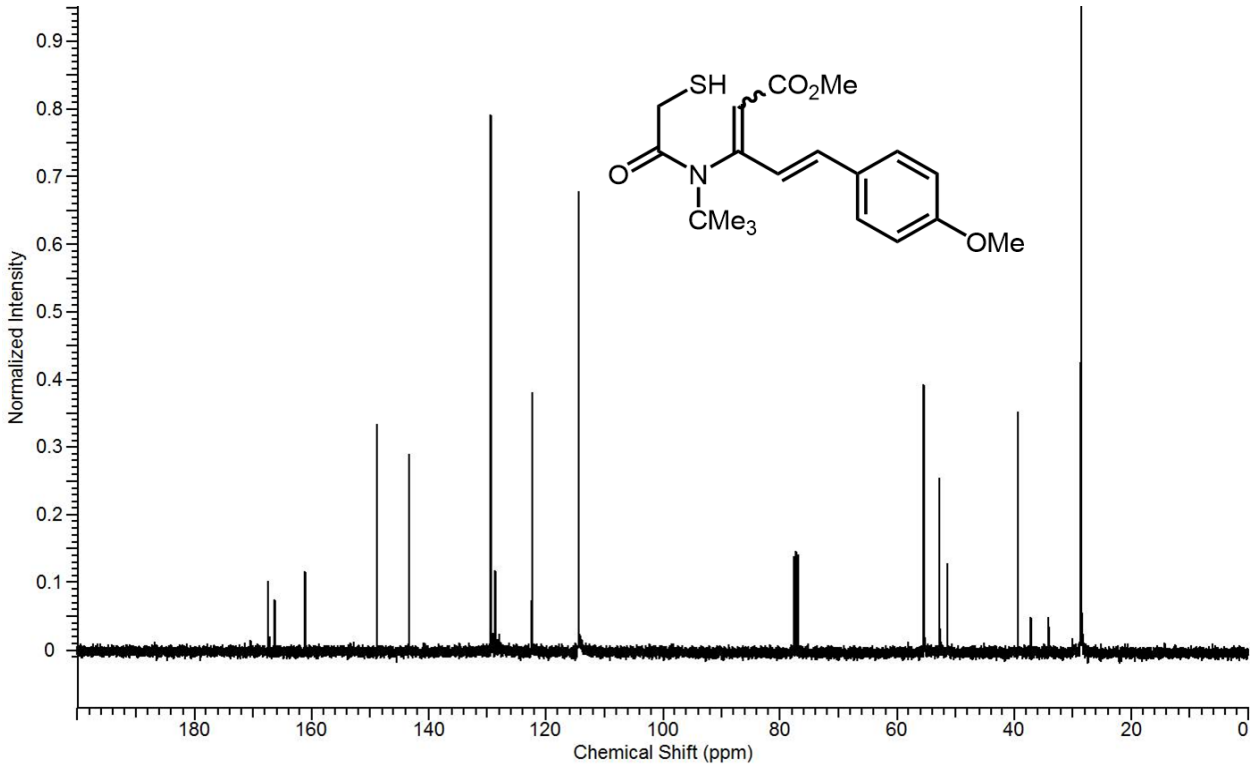
Spectrum 1-99: GC spectrum of **6b2'.**



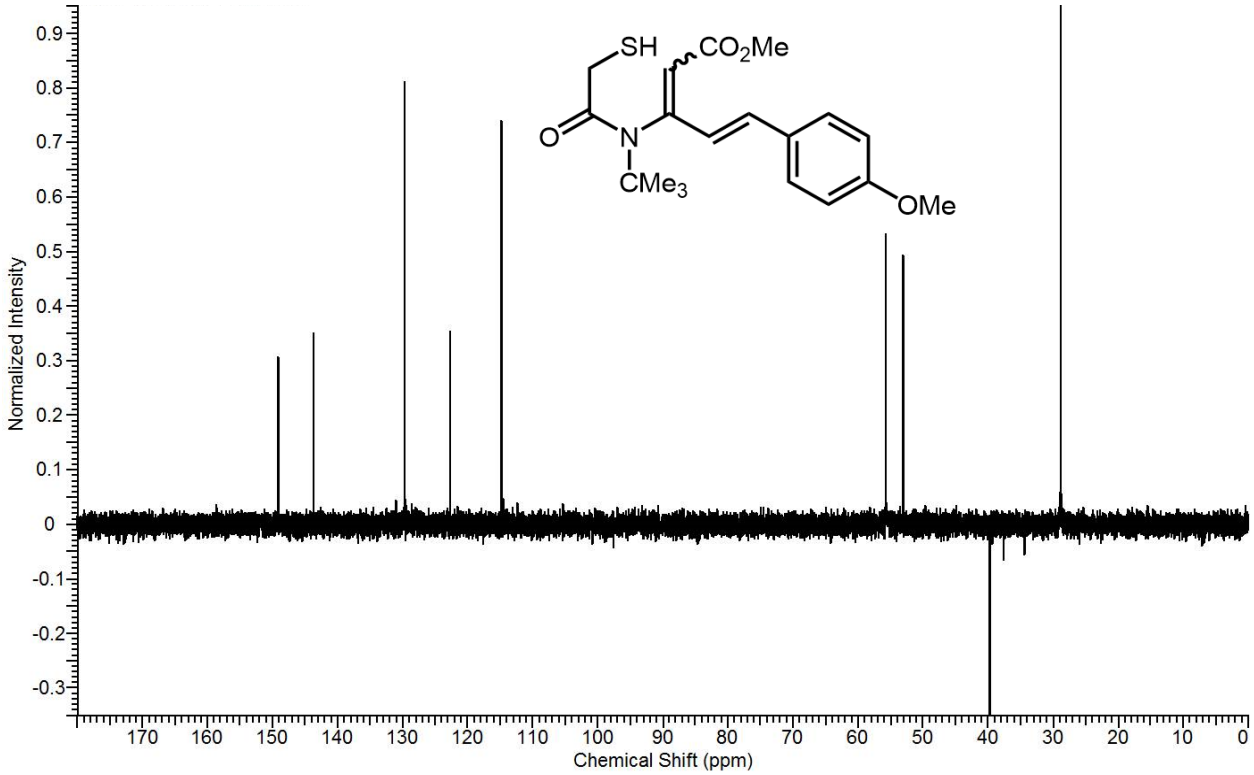
Spectrum 1-100: MS spectrum of **6b2'.**



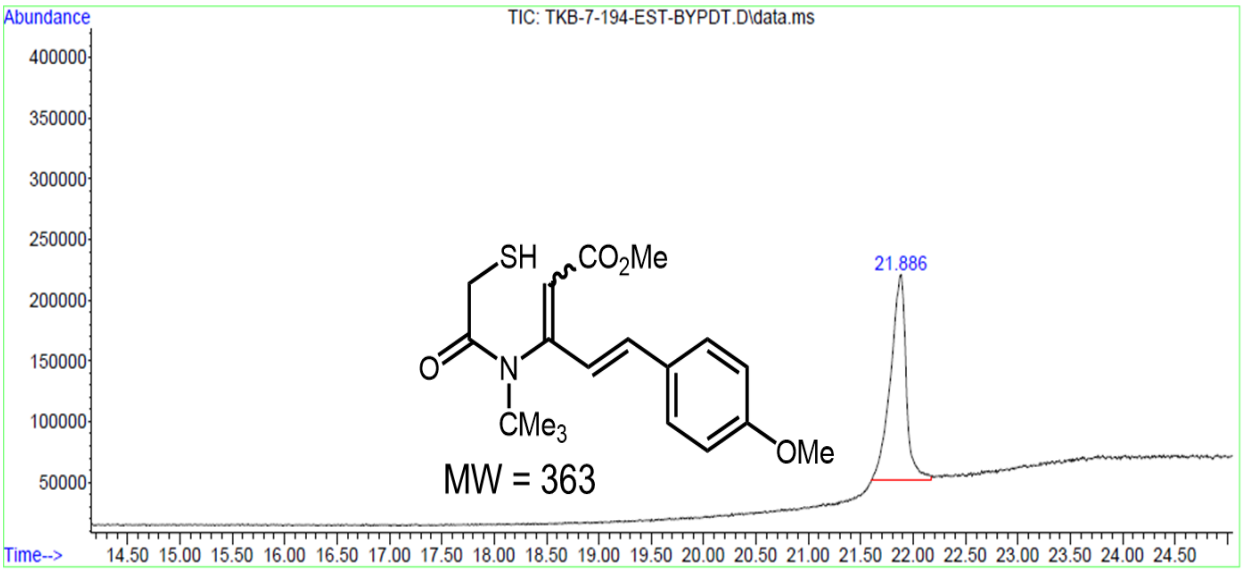
Spectrum 1-101: ^{1}H NMR spectrum of **6c2'.**

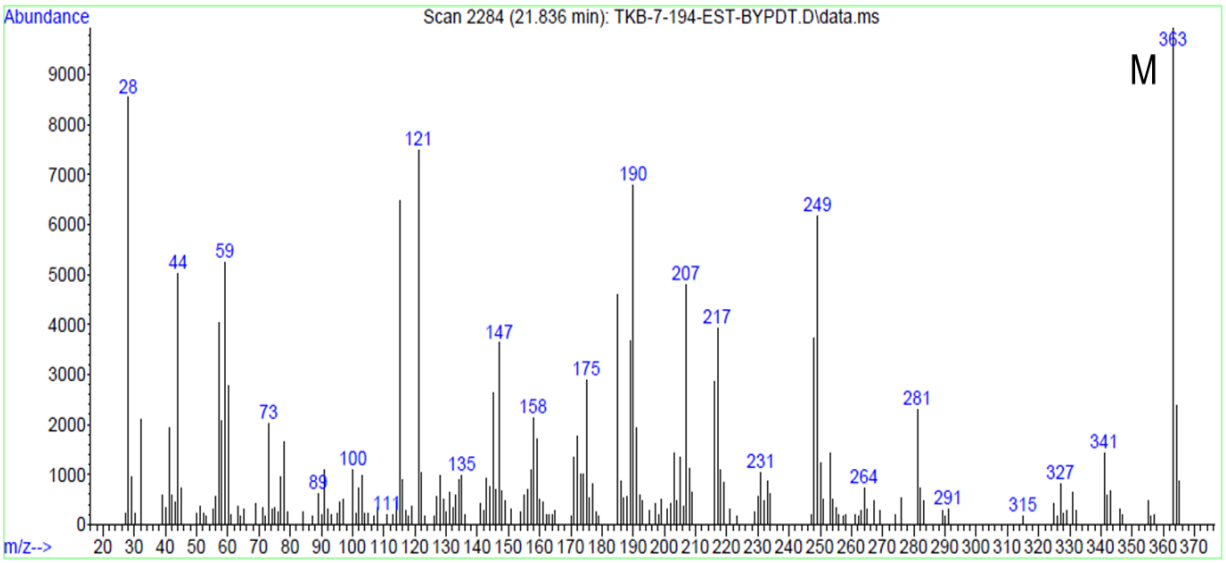


Spectrum 1-102: ^{13}C NMR spectrum of **6c2'.**

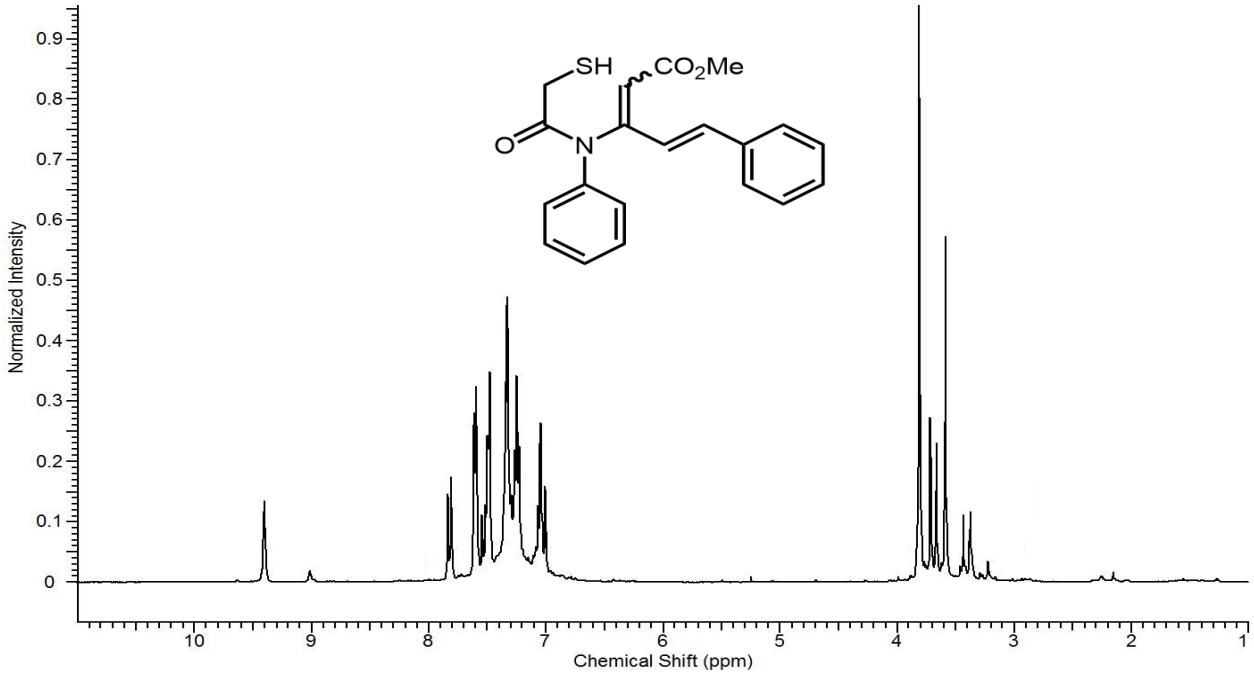


Spectrum 1-103: DEPT-135 NMR spectrum of **6c2'.**

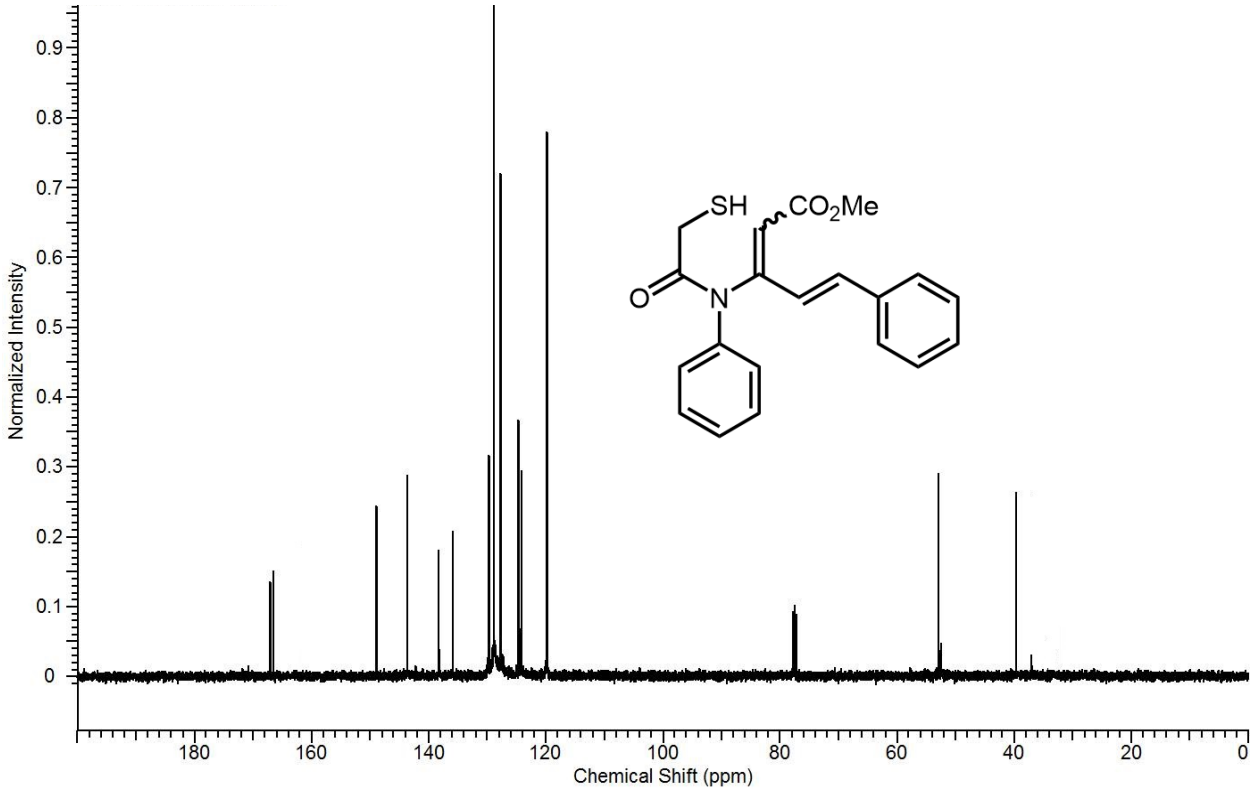




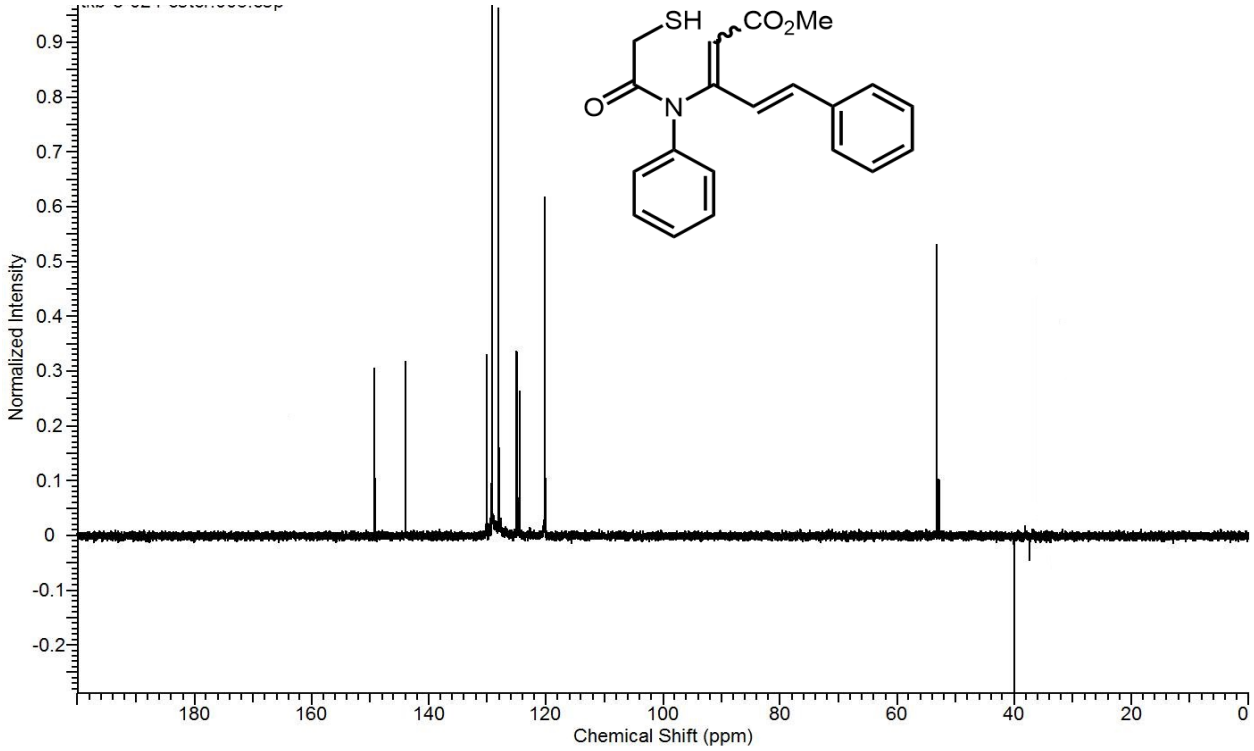
Spectrum 1-104 and 1-105: GC spectrum of **6c2'** and MS spectrum of **6c2'.**



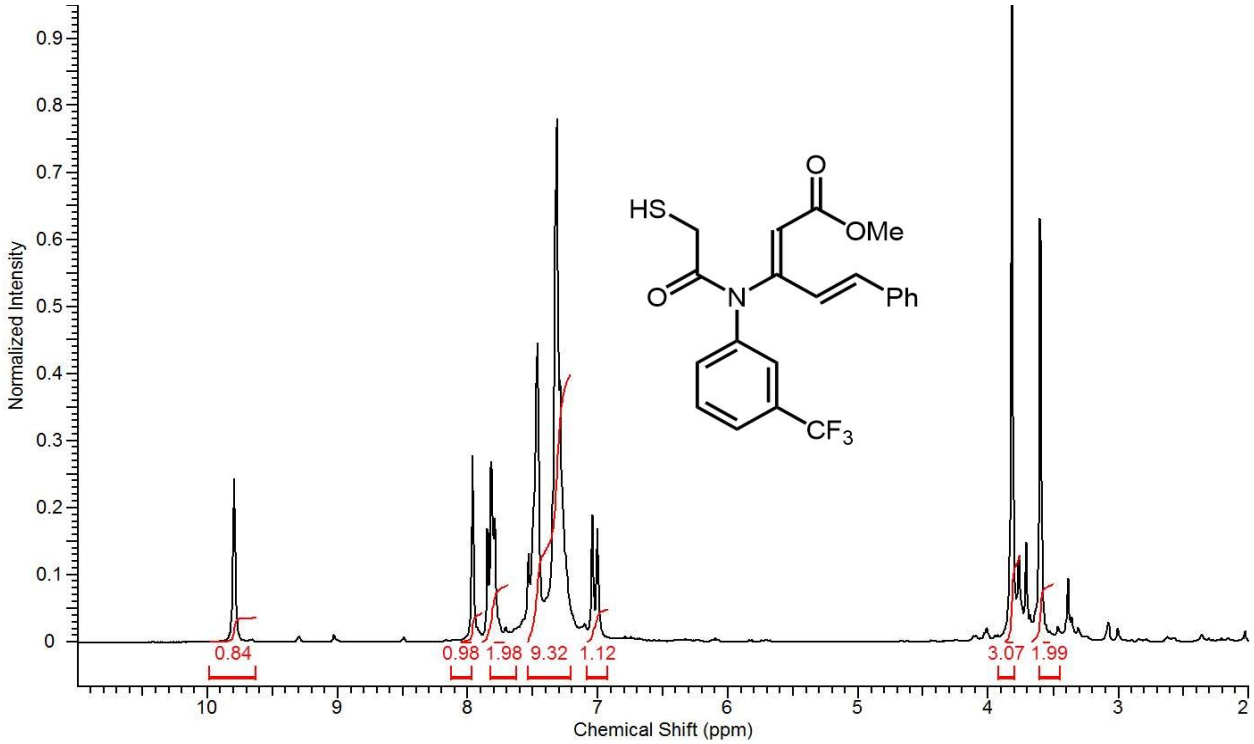
Spectrum 1-106: ^{1}H NMR spectrum of **6d2'.**



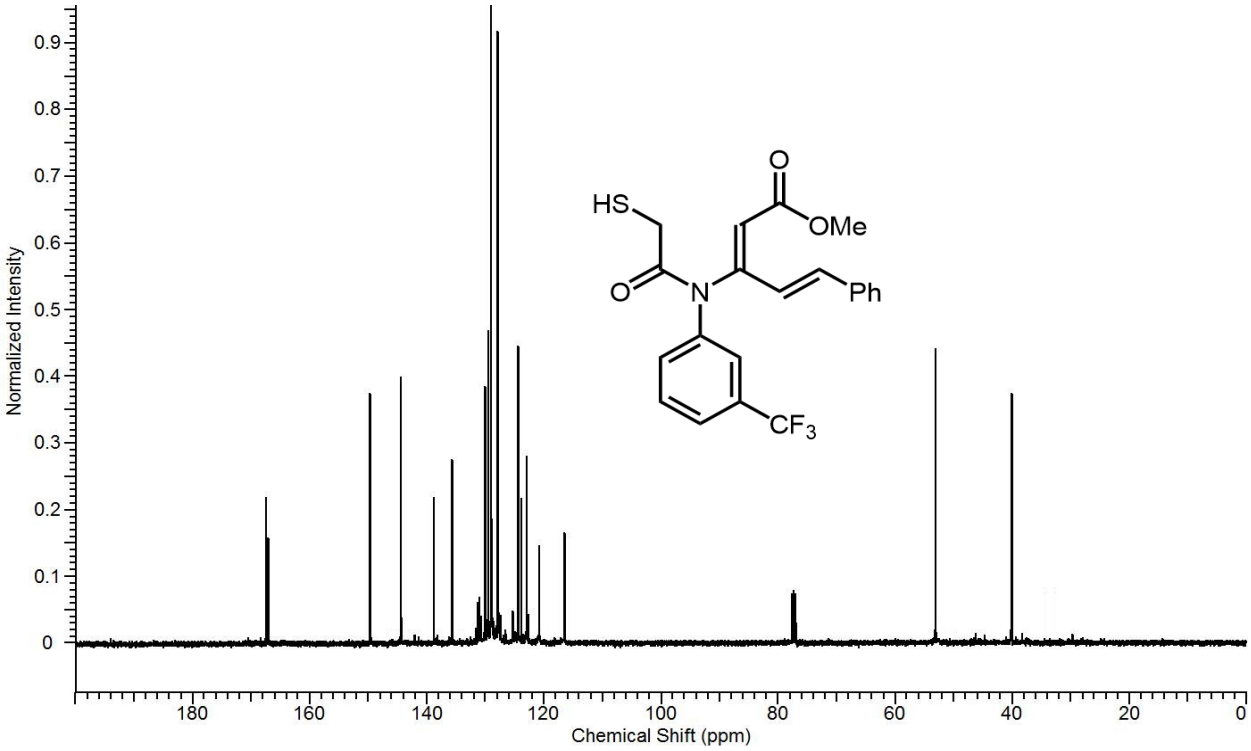
Spectrum 1-107: ^{13}C NMR spectrum of **6d2'.**



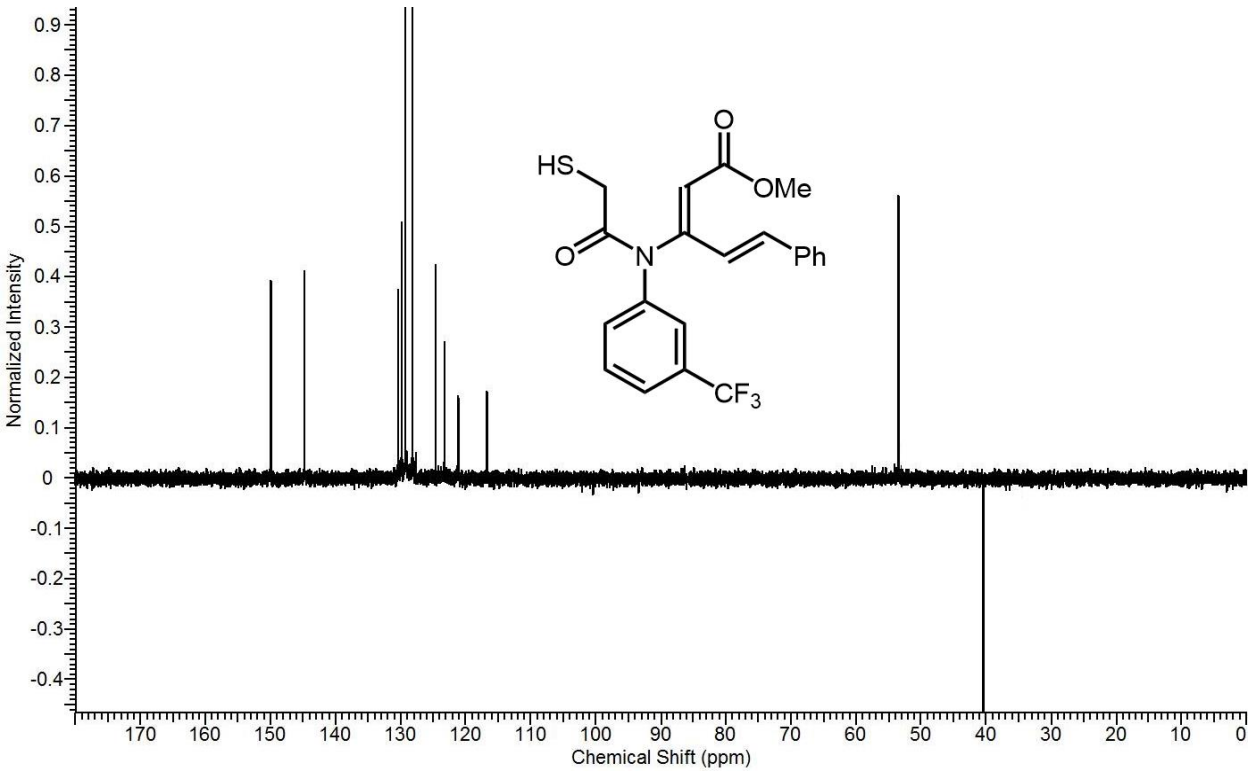
Spectrum 1-108: DEPT-135 NMR spectrum of **6d2'.**



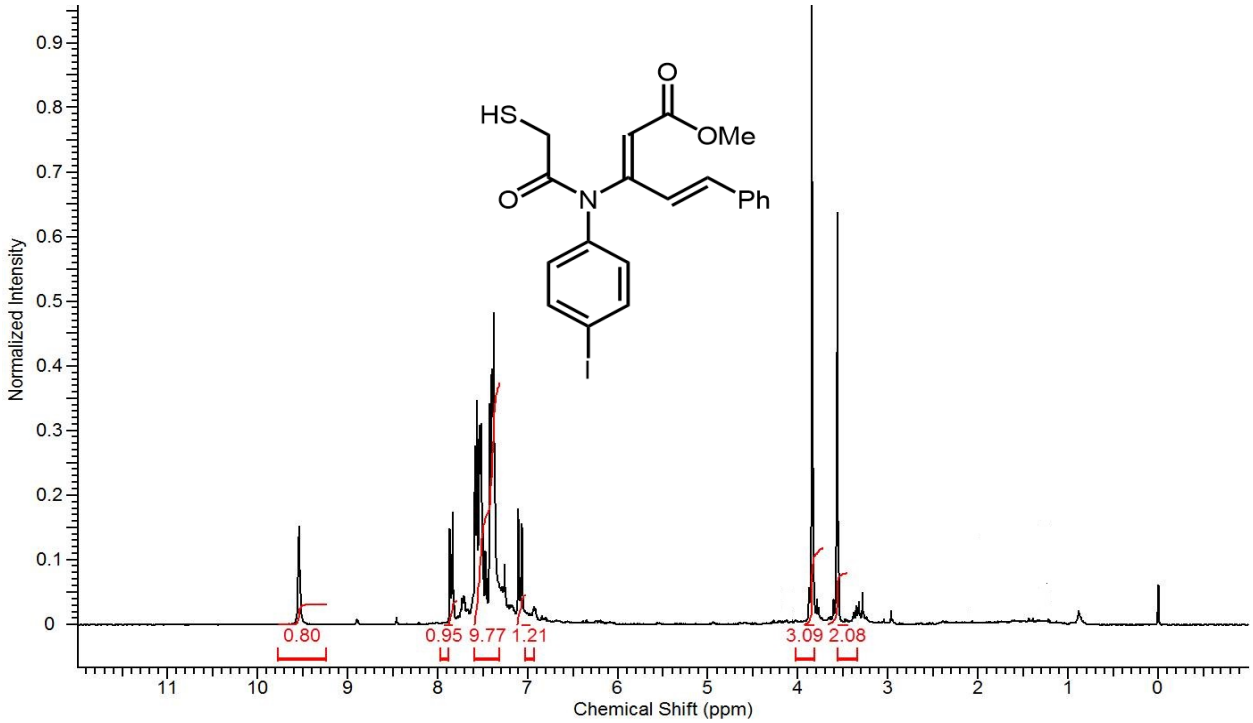
Spectrum 1-109: ^{1}H NMR spectrum of **6e2'.**



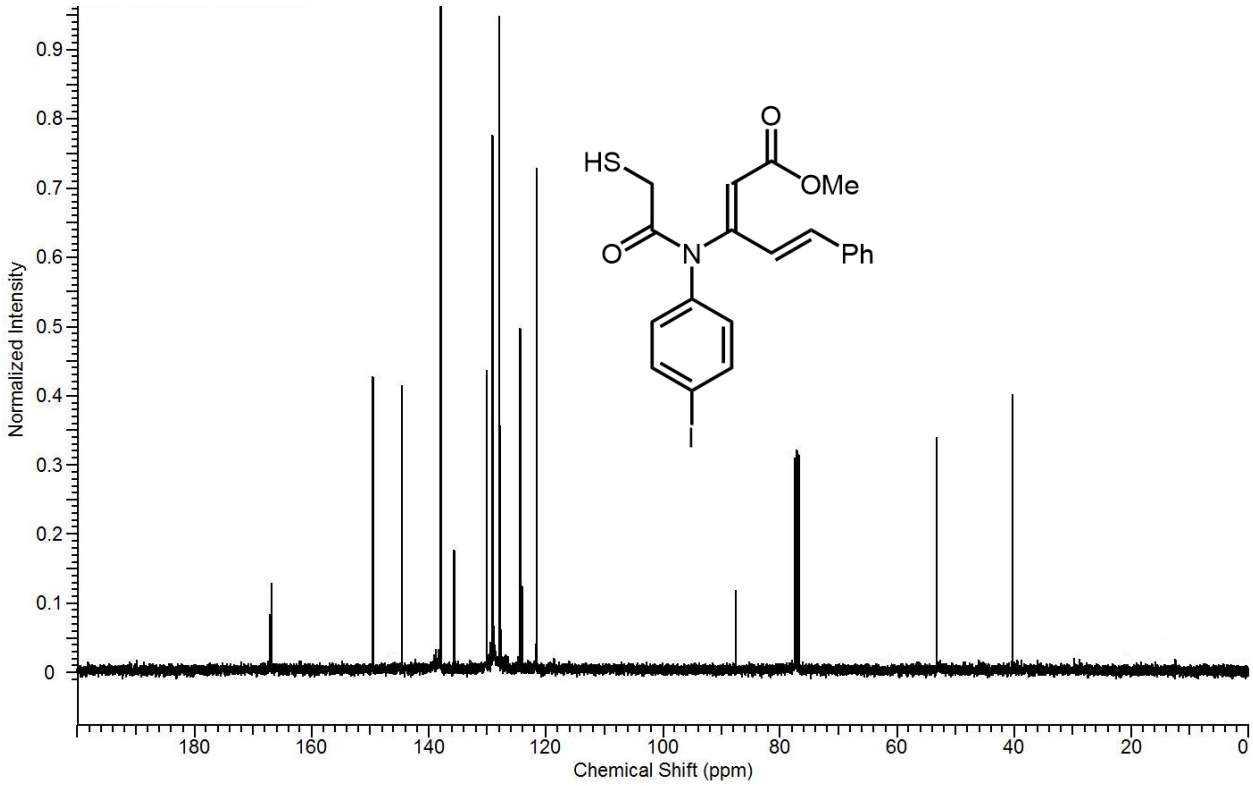
Spectrum 1-110: ^{13}C NMR spectrum of **6e2'.**



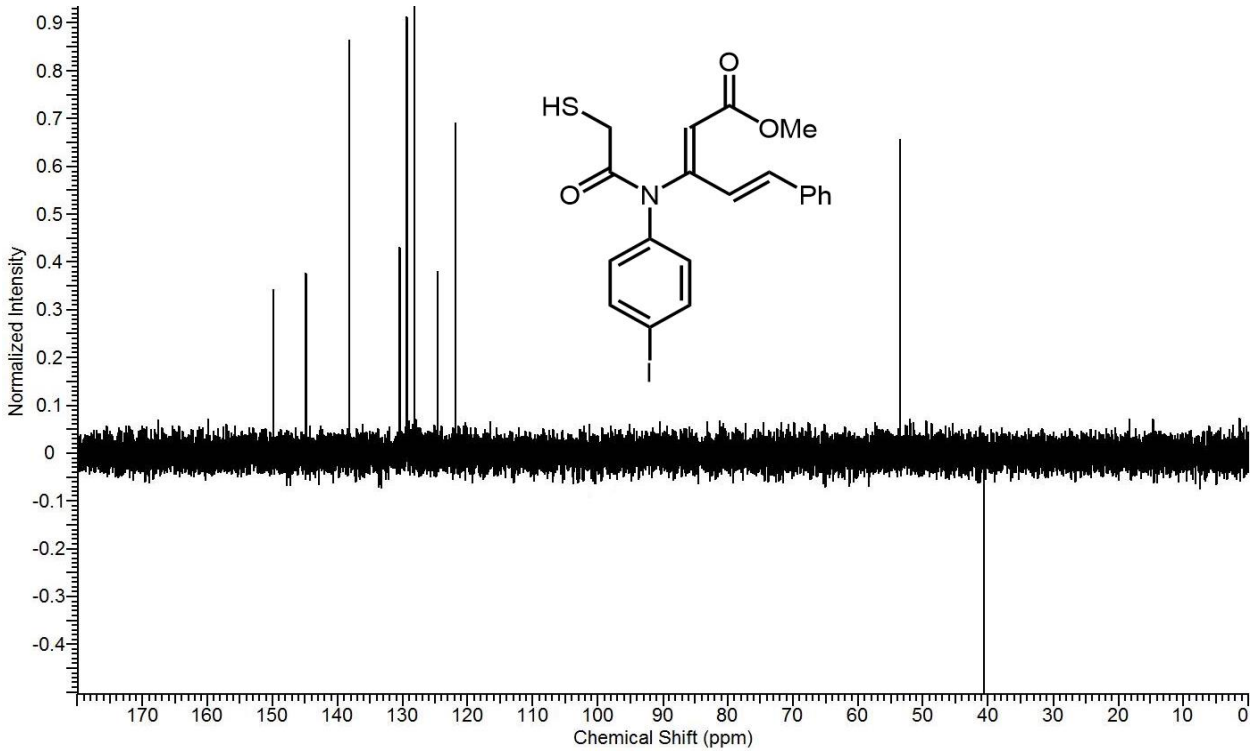
Spectrum 1-111: DEPT-135 NMR spectrum of **6e2'.**



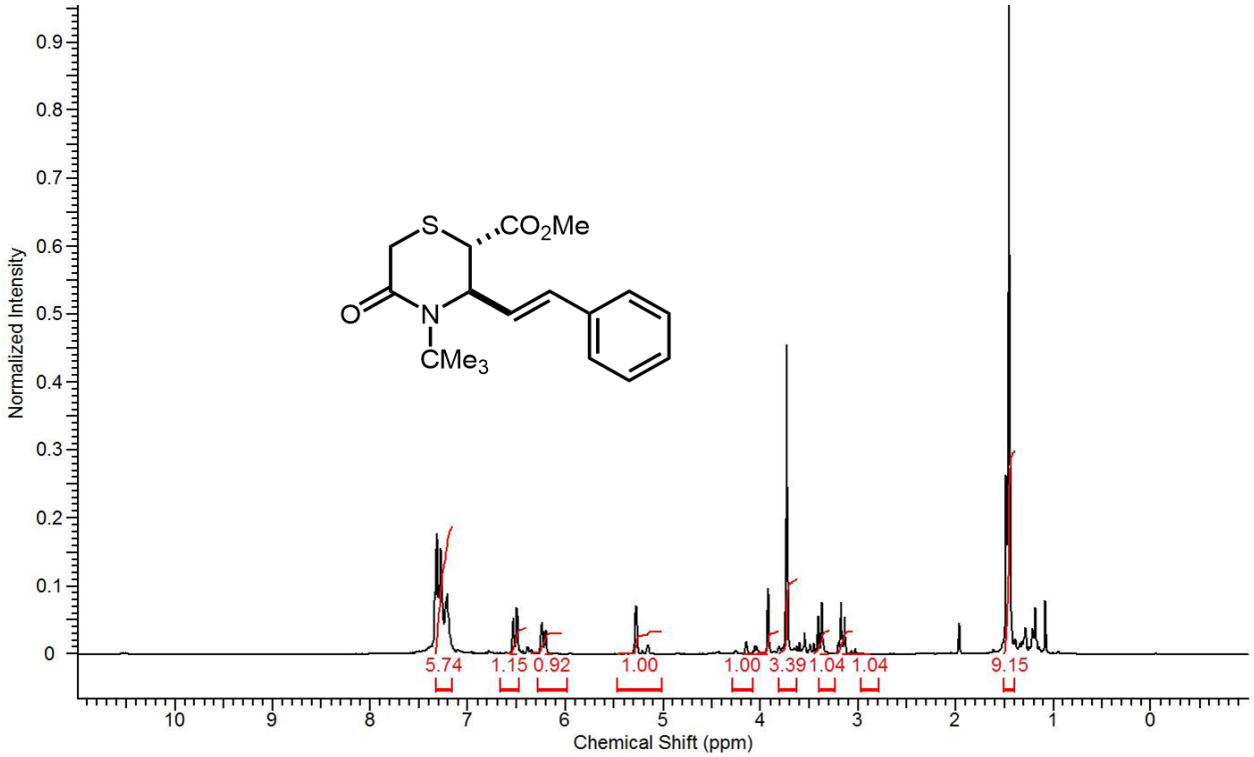
Spectrum 1-112: ^{1}H NMR spectrum of **6f2'.**



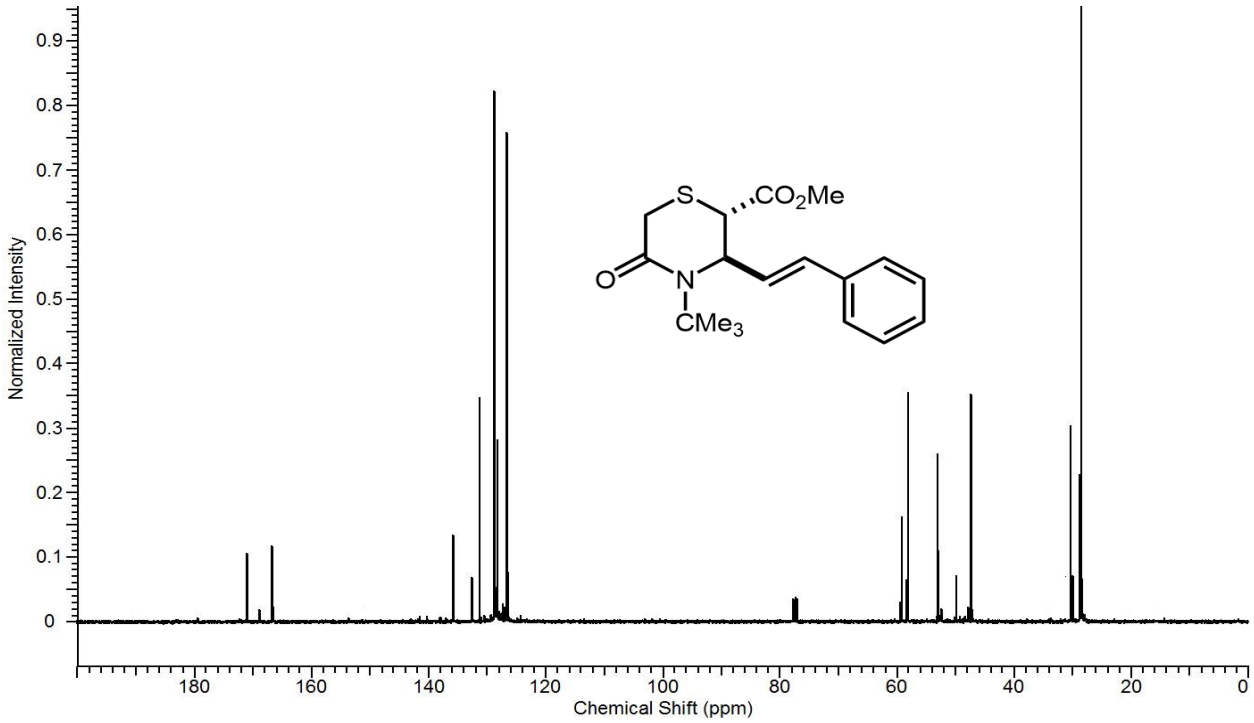
Spectrum 1-113: ^{13}C NMR spectrum of **6f2'.**



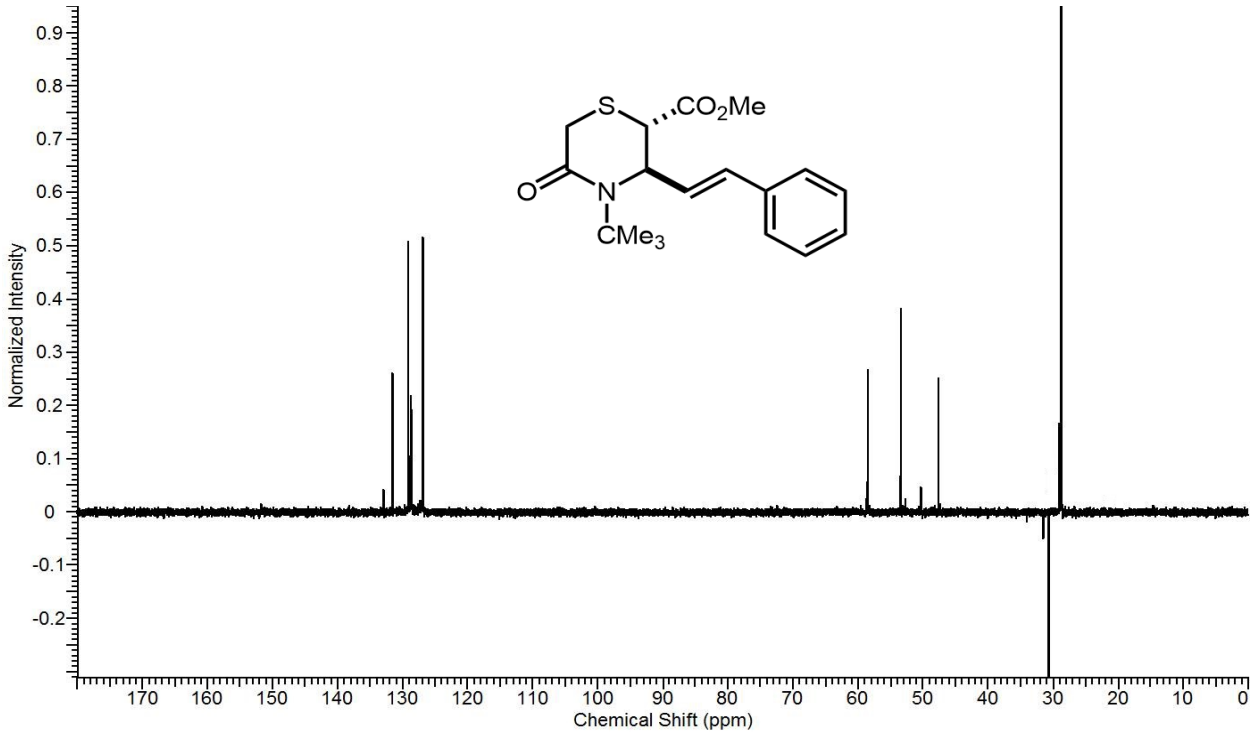
Spectrum 1-114: DEPT-135 NMR spectrum of **6f2'.**



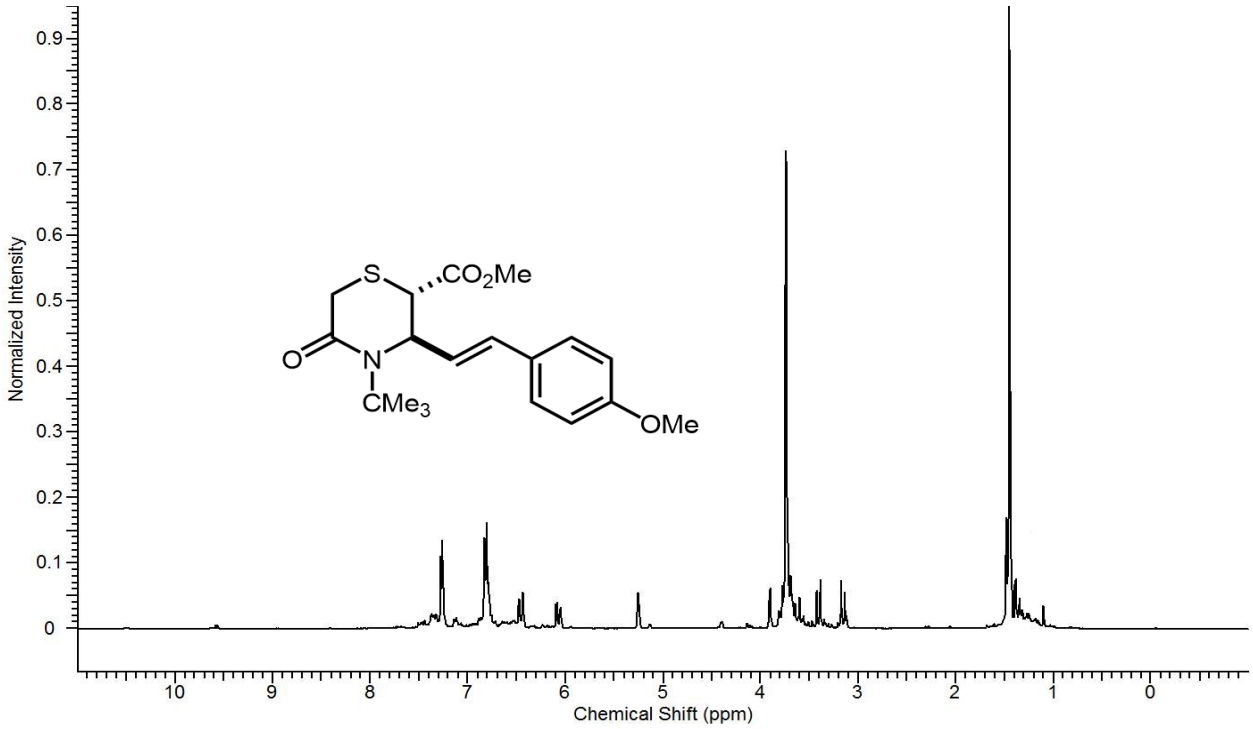
Spectrum 1-115: ^{1}H NMR spectrum of **6b2.**



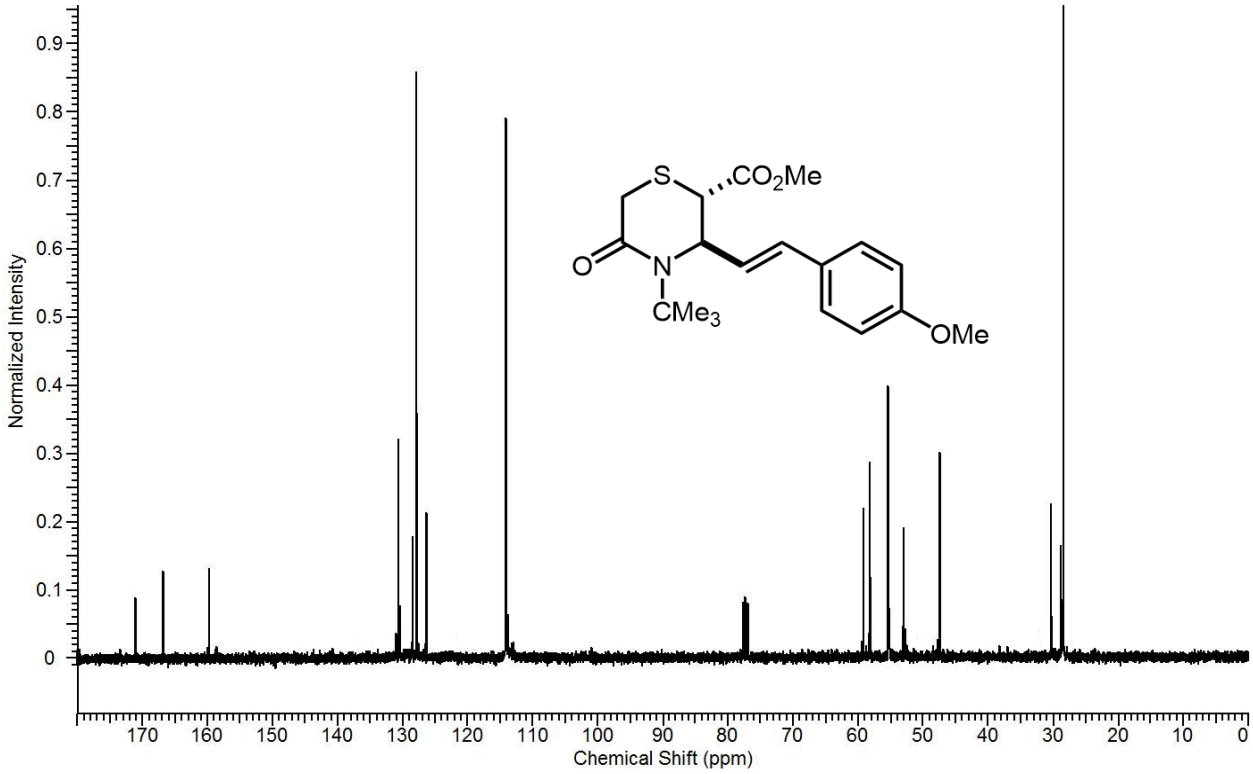
Spectrum 1-116: ^{13}C NMR spectrum of **6b2.**



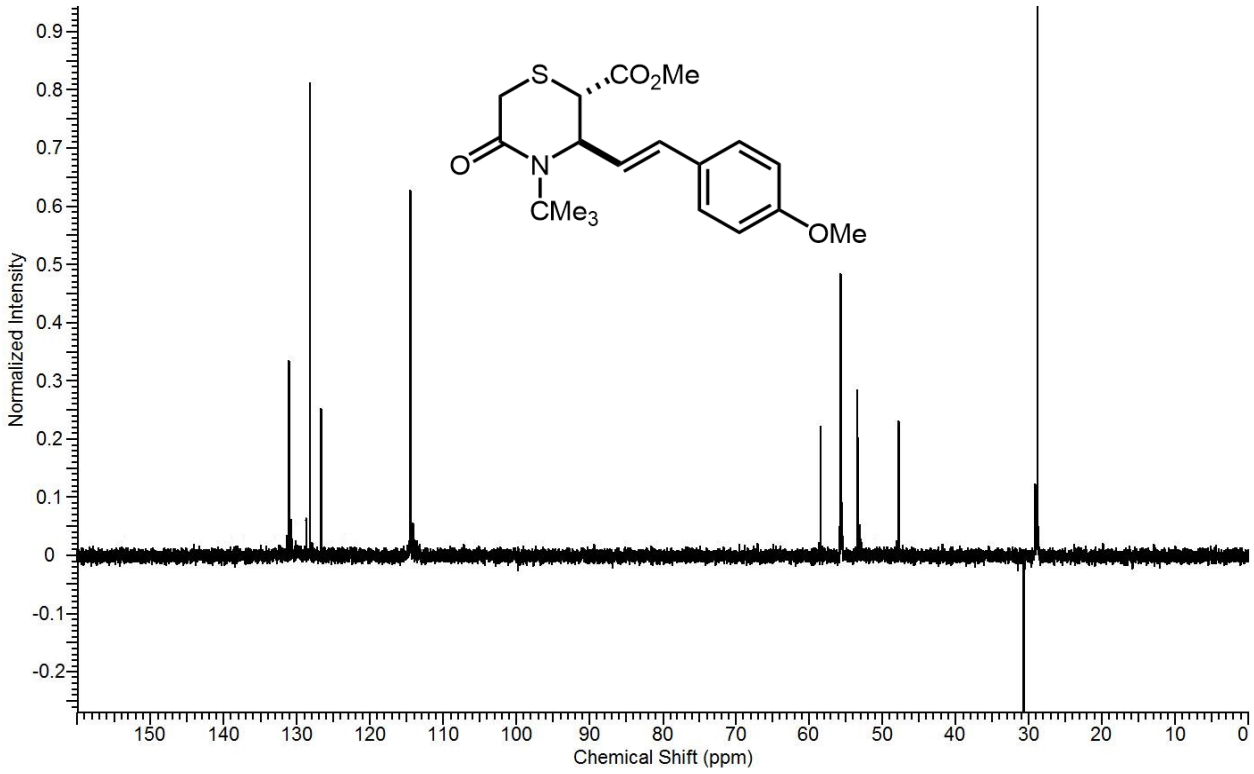
Spectrum 1-117: DEPT-135 NMR spectrum of **6b2.**



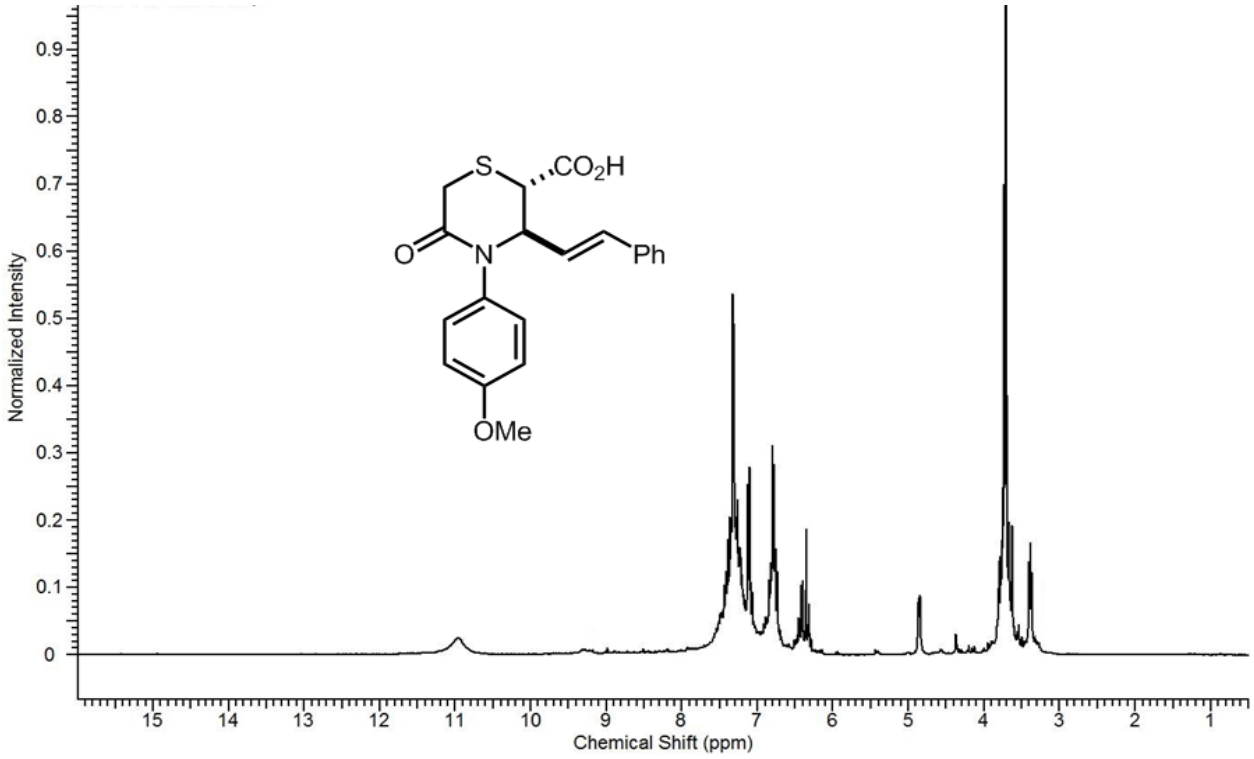
Spectrum 1-118: ^{1}H NMR spectrum of **6c2.**



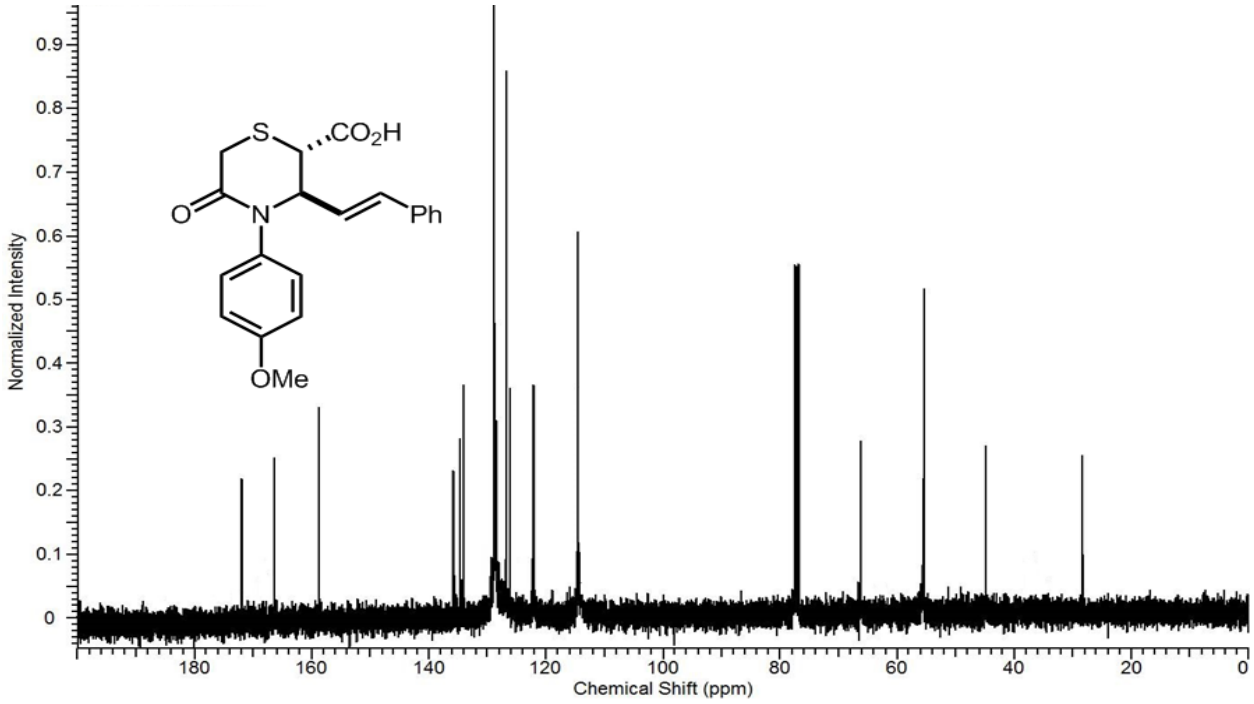
Spectrum 1-119: ^{13}C NMR spectrum of **6c2.**



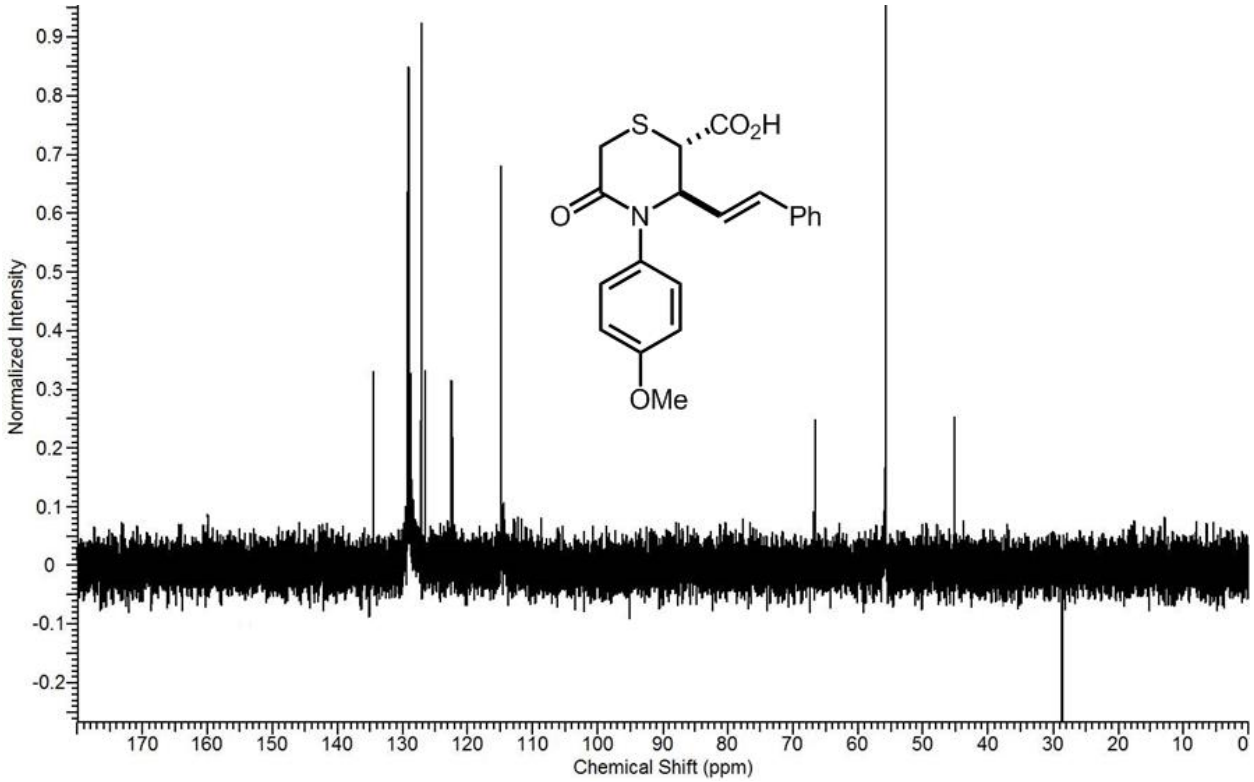
Spectrum 1-120: DEPT-135 NMR spectrum of **6c2.**



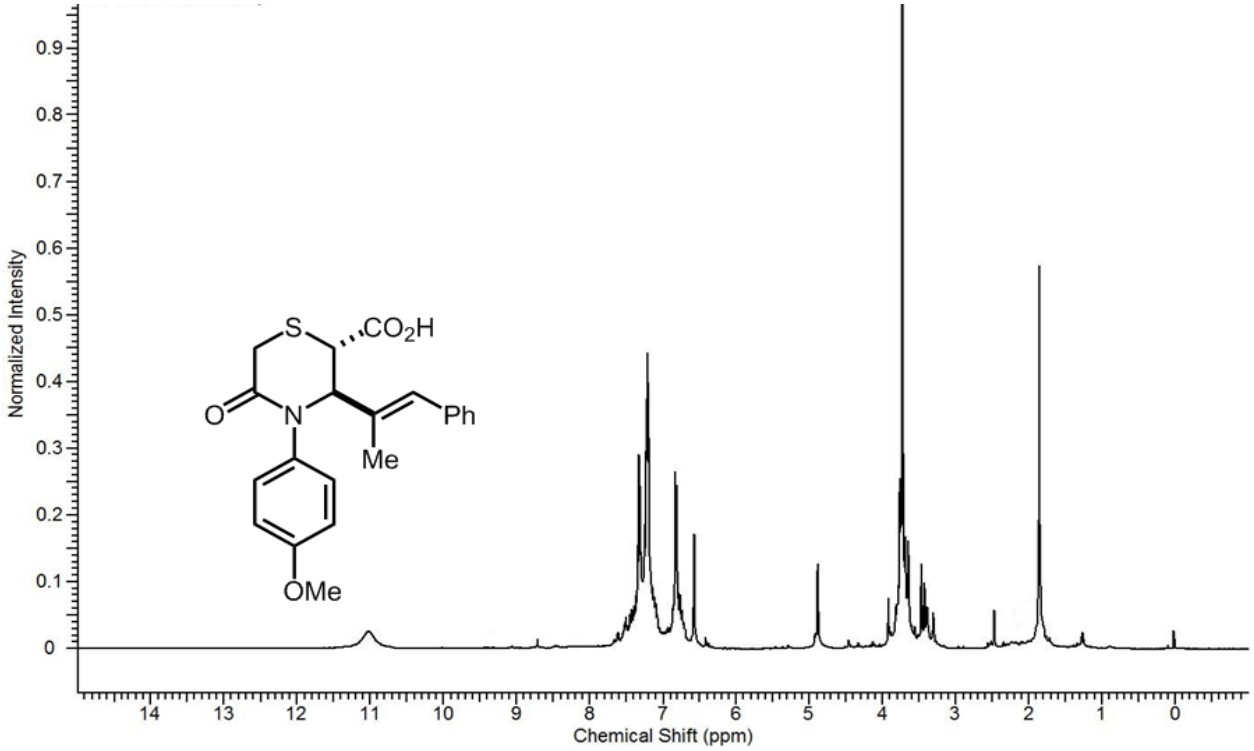
Spectrum 1-121: ^{1}H NMR spectrum of **6g1.**



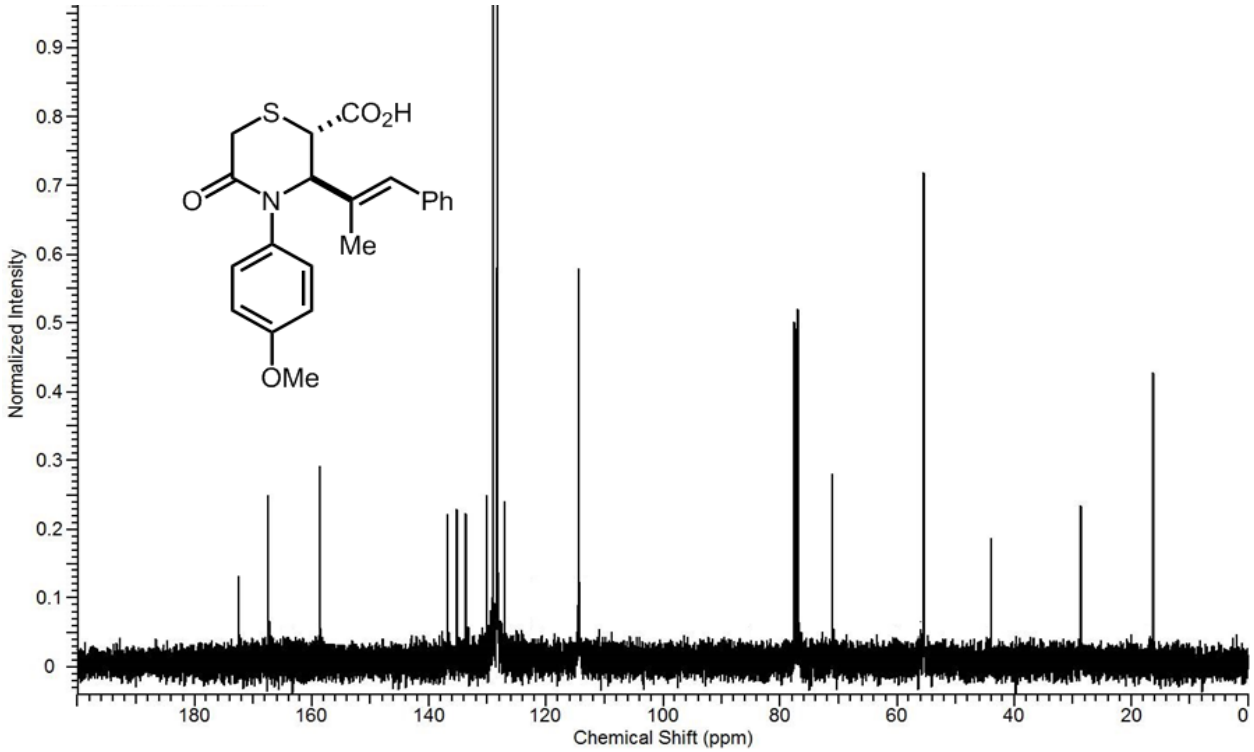
Spectrum 1-122: ^{13}C NMR spectrum of **6g1.**



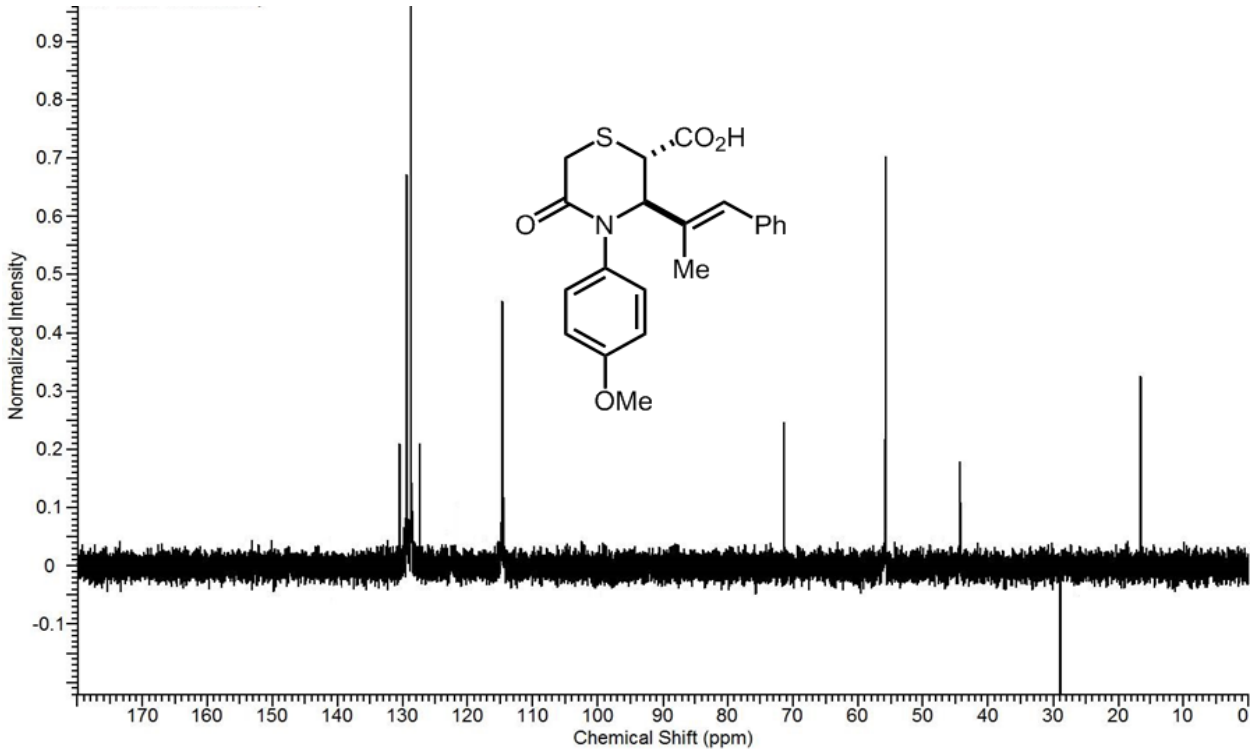
Spectrum 1-123: DEPT-135 NMR spectrum of **6g1.**



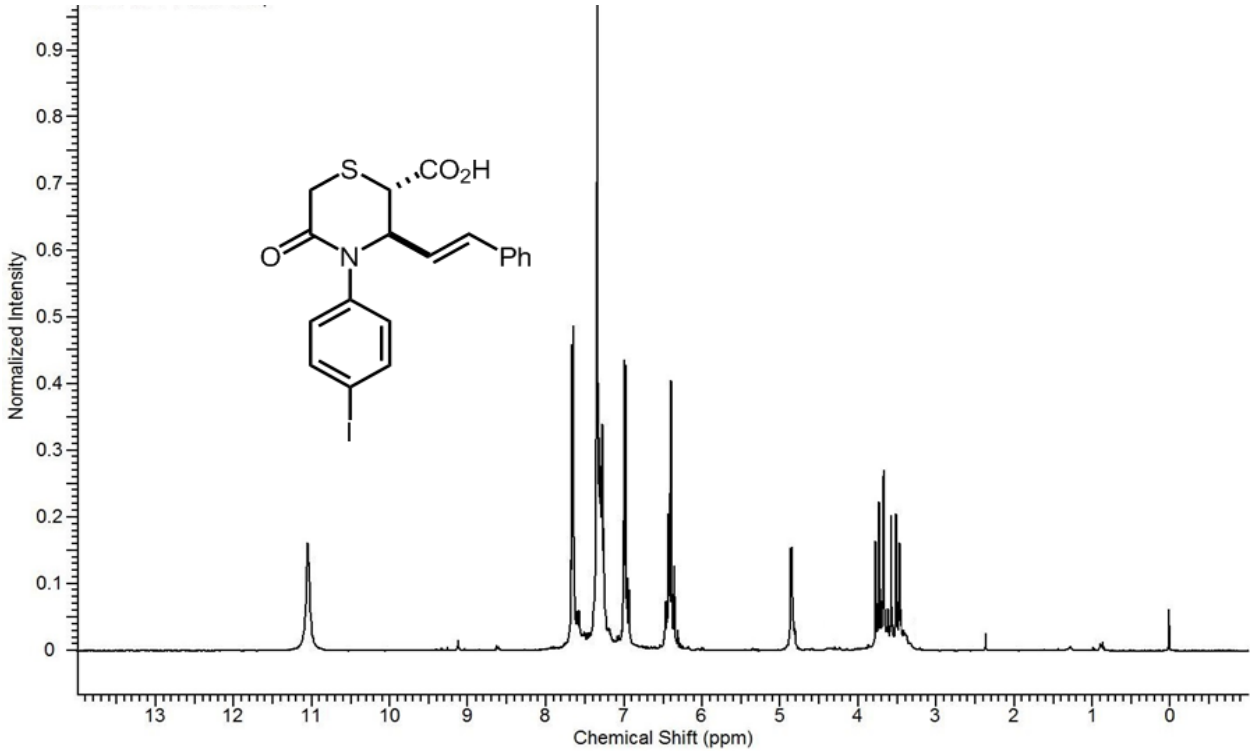
Spectrum 1-124: ^{1}H NMR spectrum of **61H.**



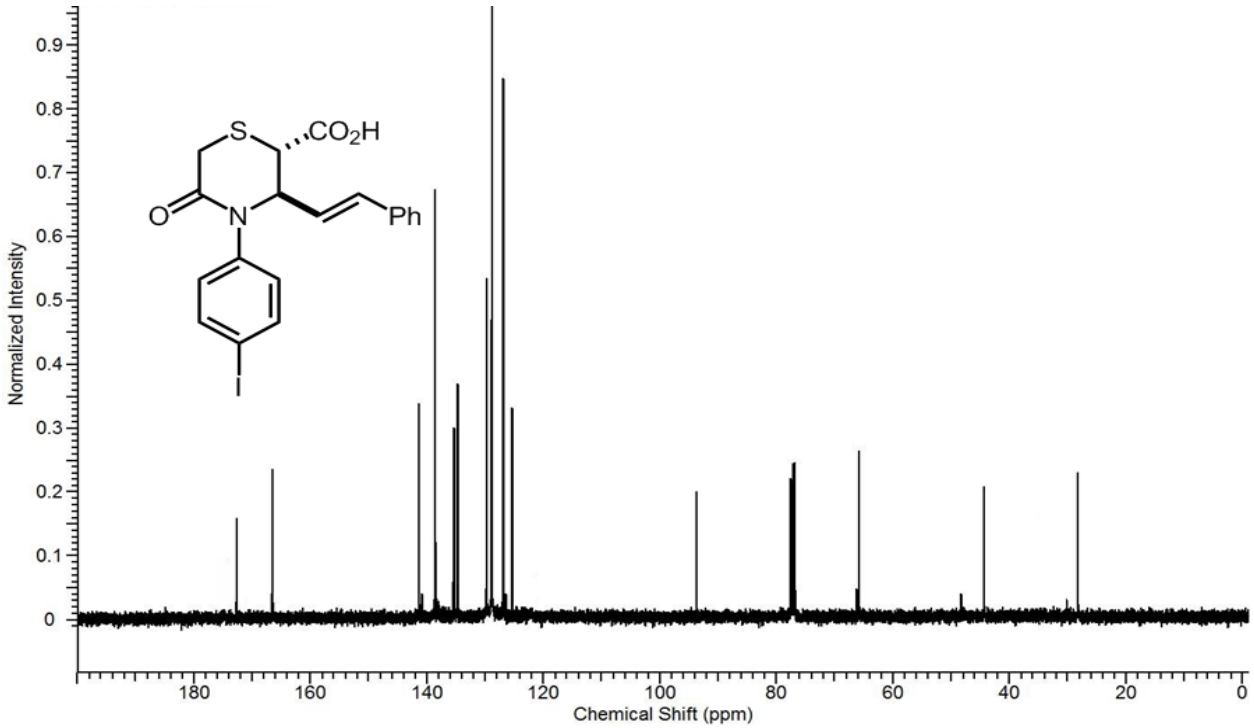
Spectrum 1-125: ^{13}C NMR spectrum of **61H.**



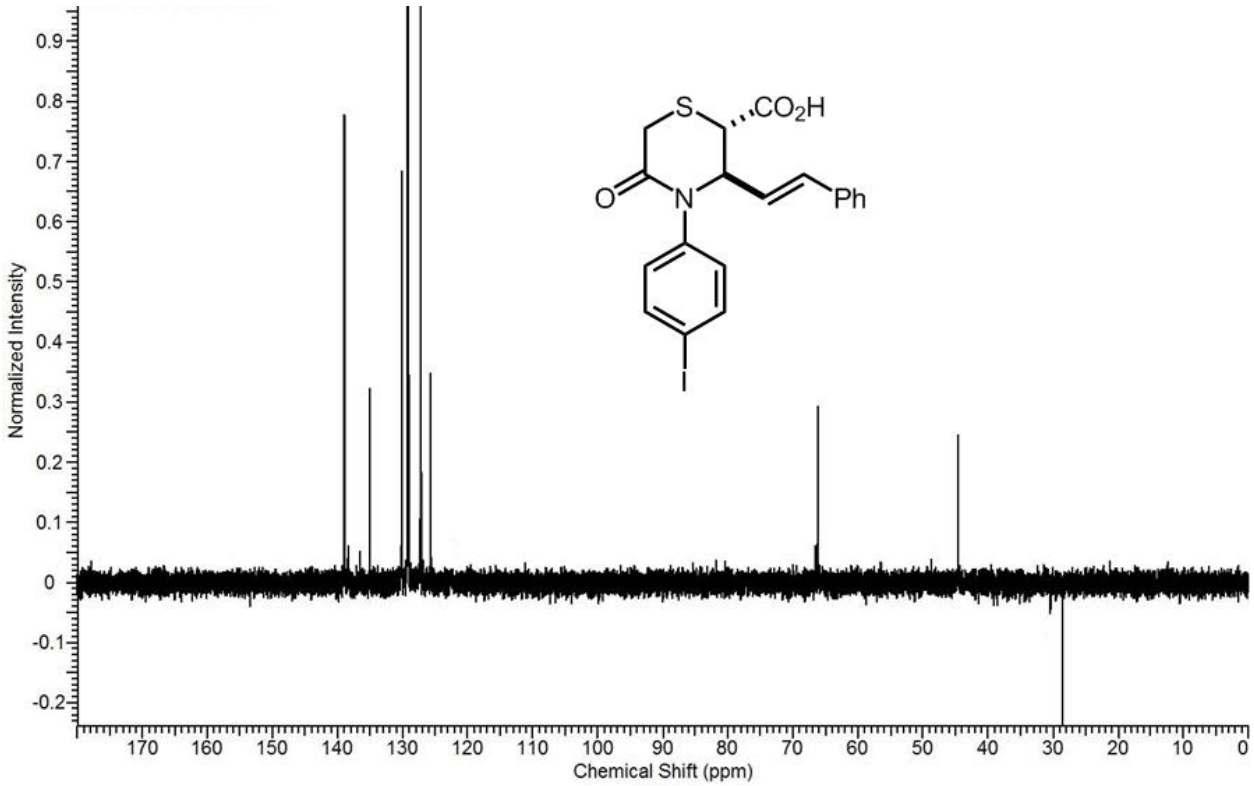
Spectrum 1-126: DEPT-135 NMR spectrum of **61H.**



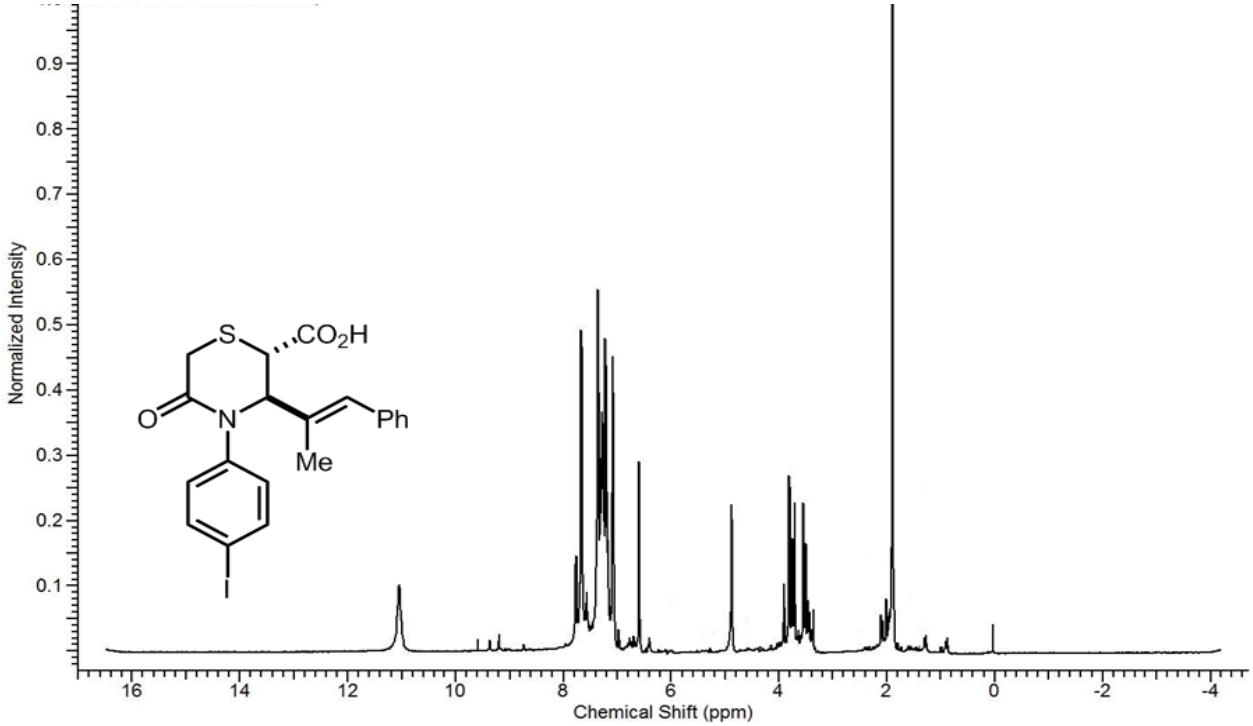
Spectrum 1-127: ^{1}H NMR spectrum of **6f1.**



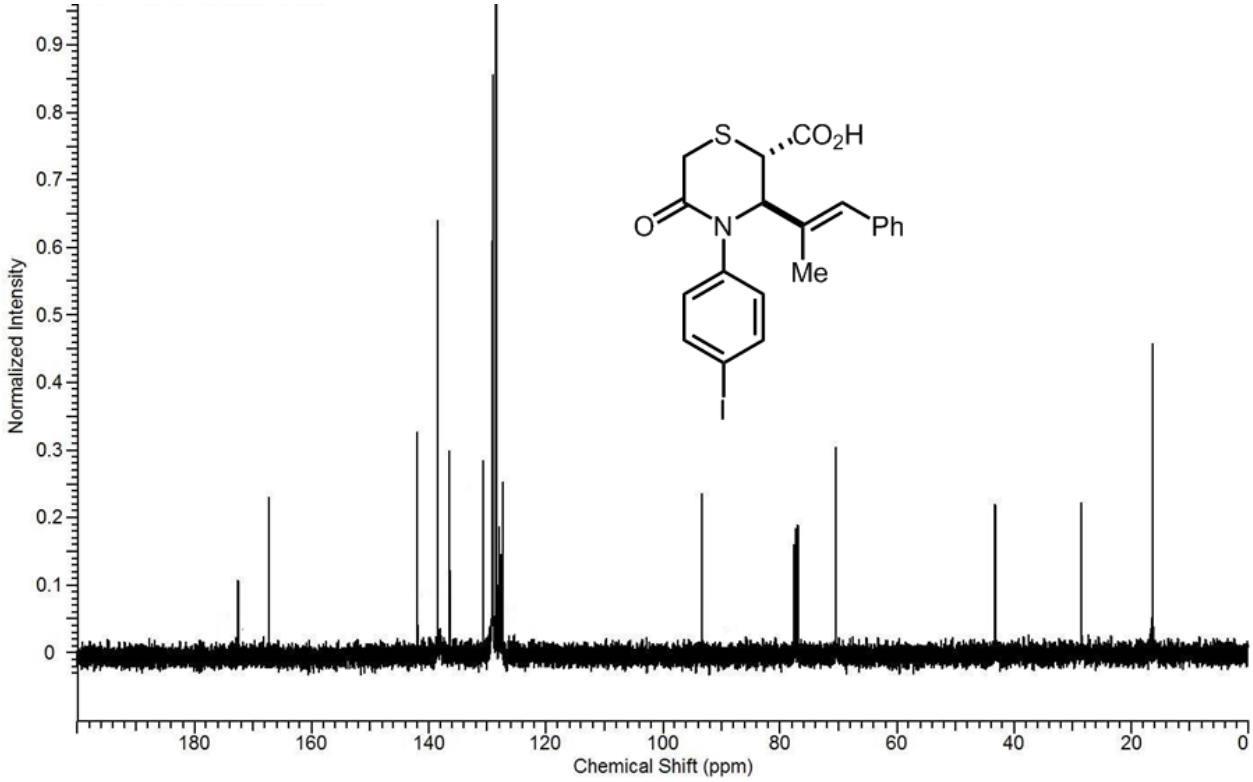
Spectrum 1-128: ^{13}C NMR spectrum of **6f1.**



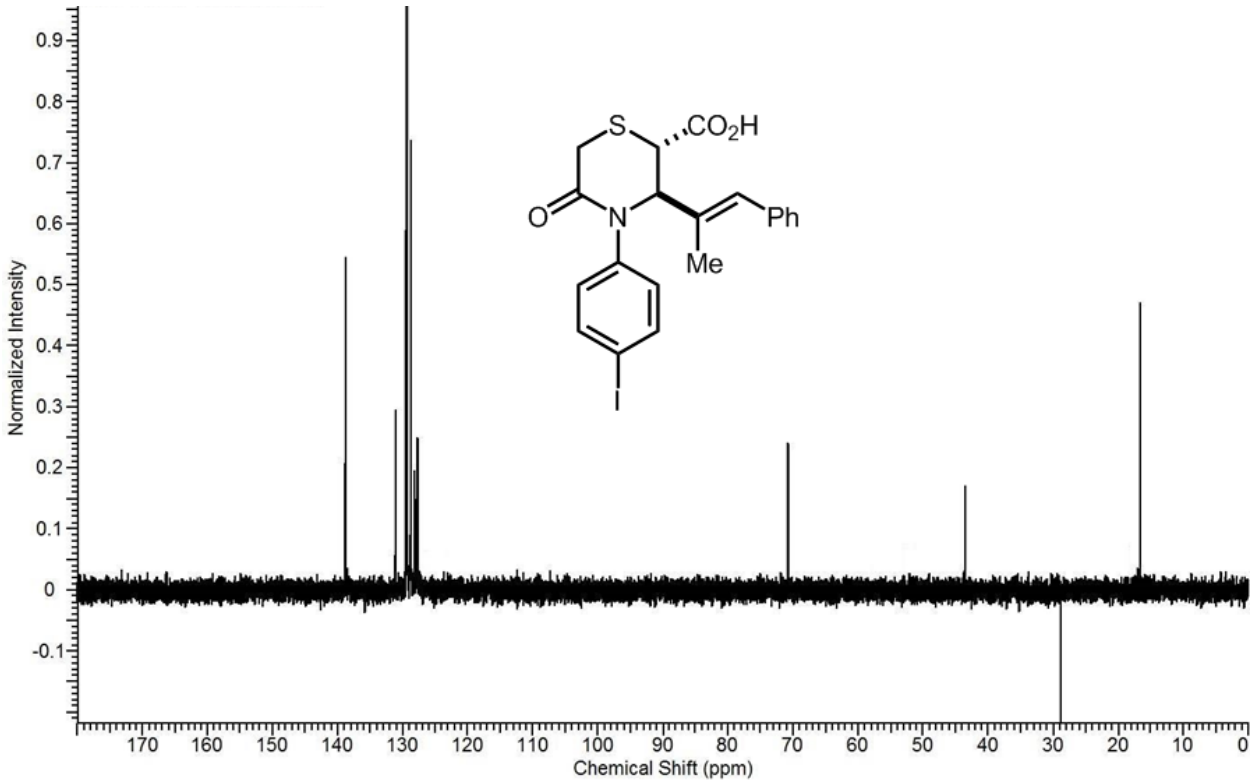
Spectrum 1-129: DEPT-135 NMR spectrum of **6f1.**



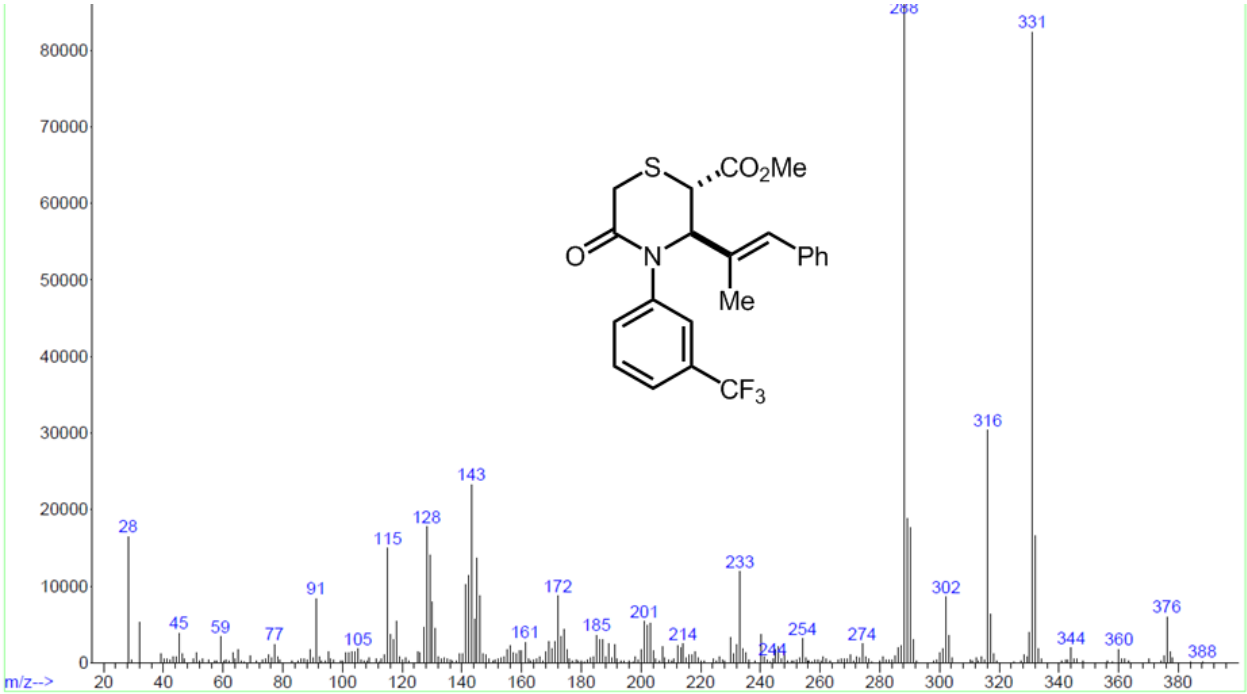
Spectrum 1-130: ^{1}H NMR spectrum of **6i1.**



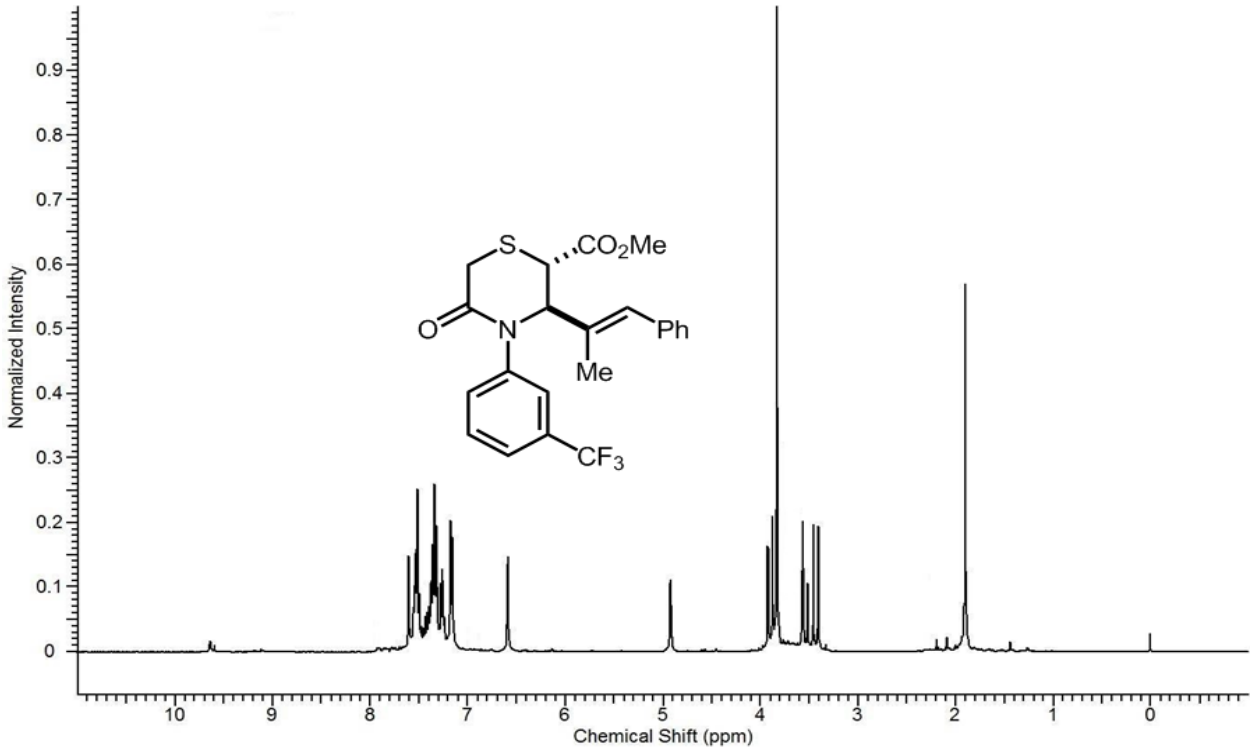
Spectrum 1-131: ^{13}C NMR spectrum of **6i1.**



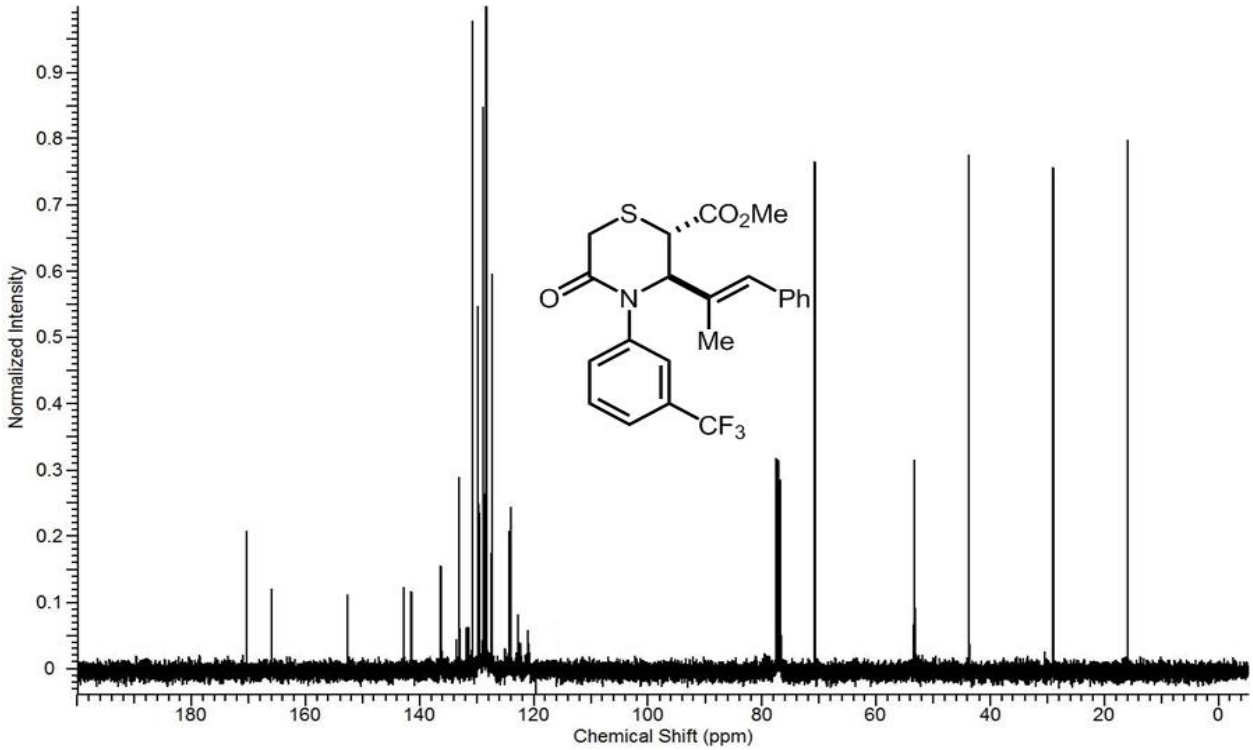
Spectrum 1-132: DEPT-135 NMR spectrum of **6i1.**



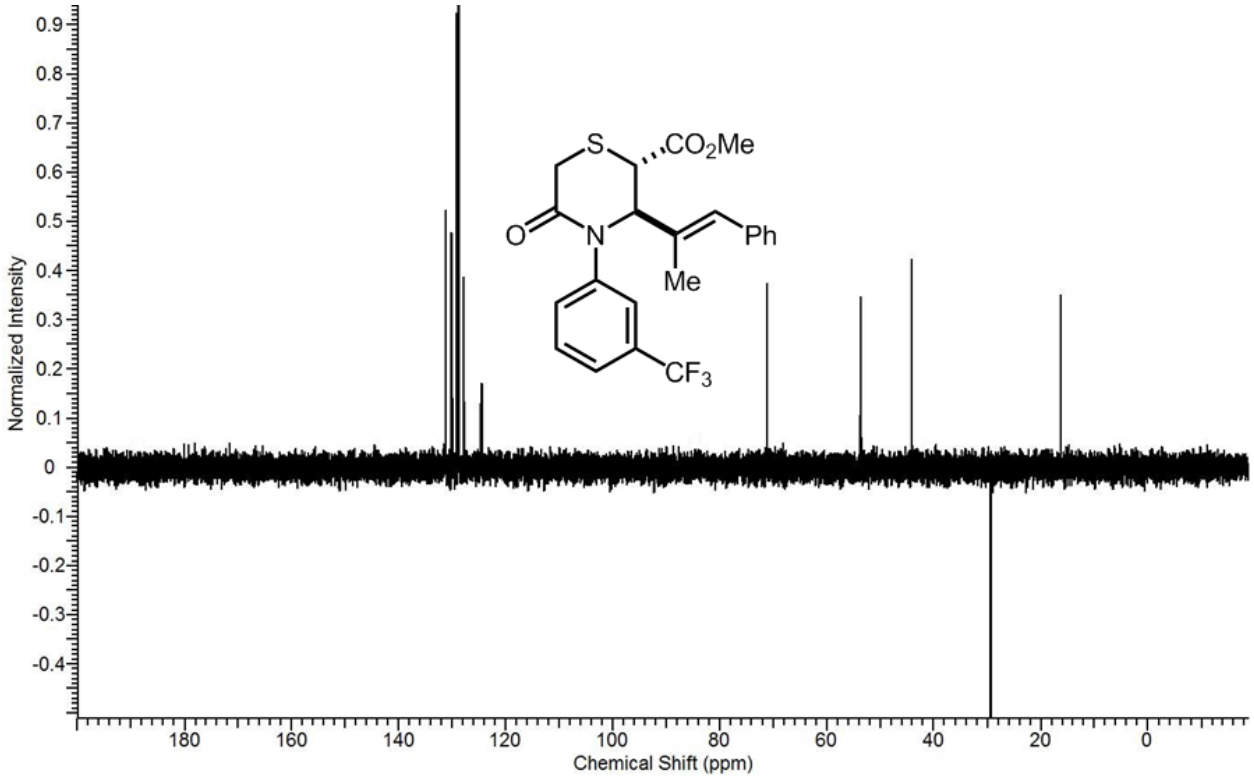
Spectrum 1-133: MS spectrum of **6j2.**



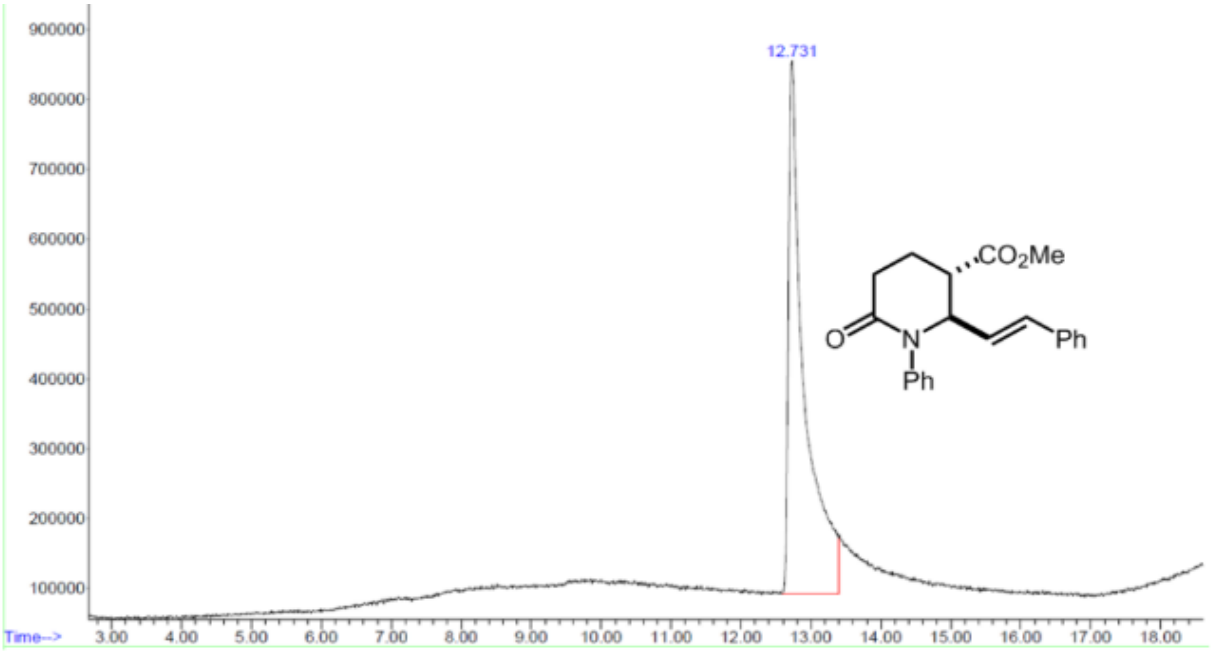
Spectrum 1-134: ^{1}H NMR spectrum of **6j2.**



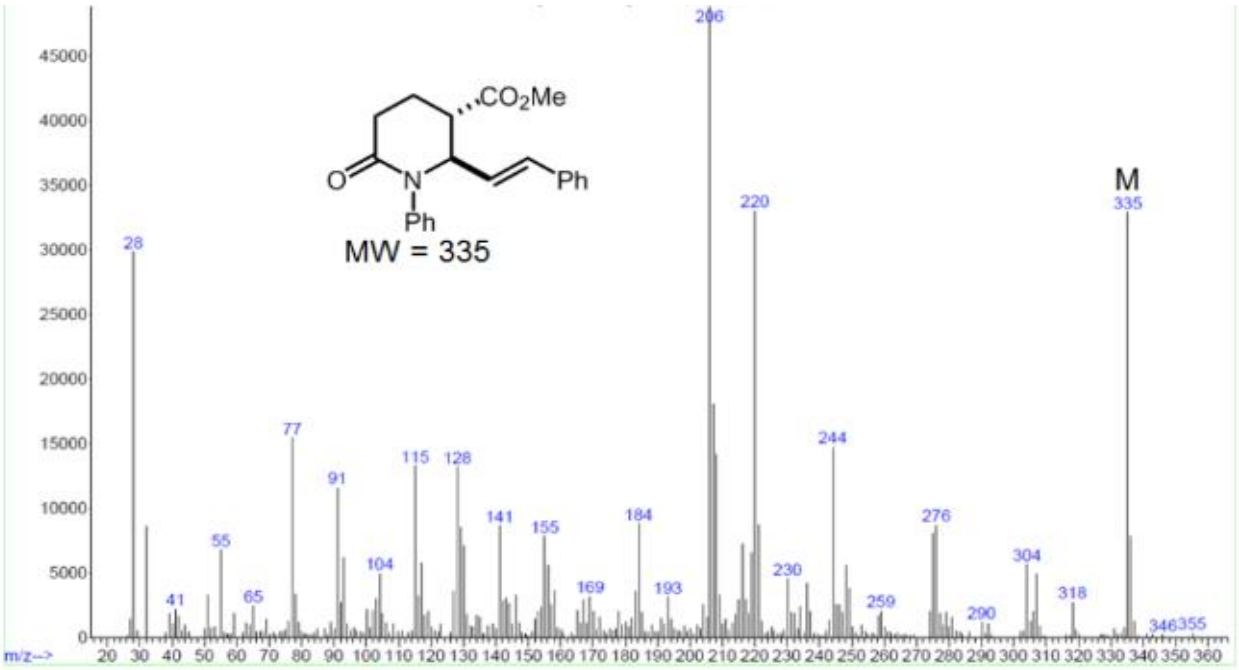
Spectrum 1-135: ^{13}C NMR spectrum of **6j2.**



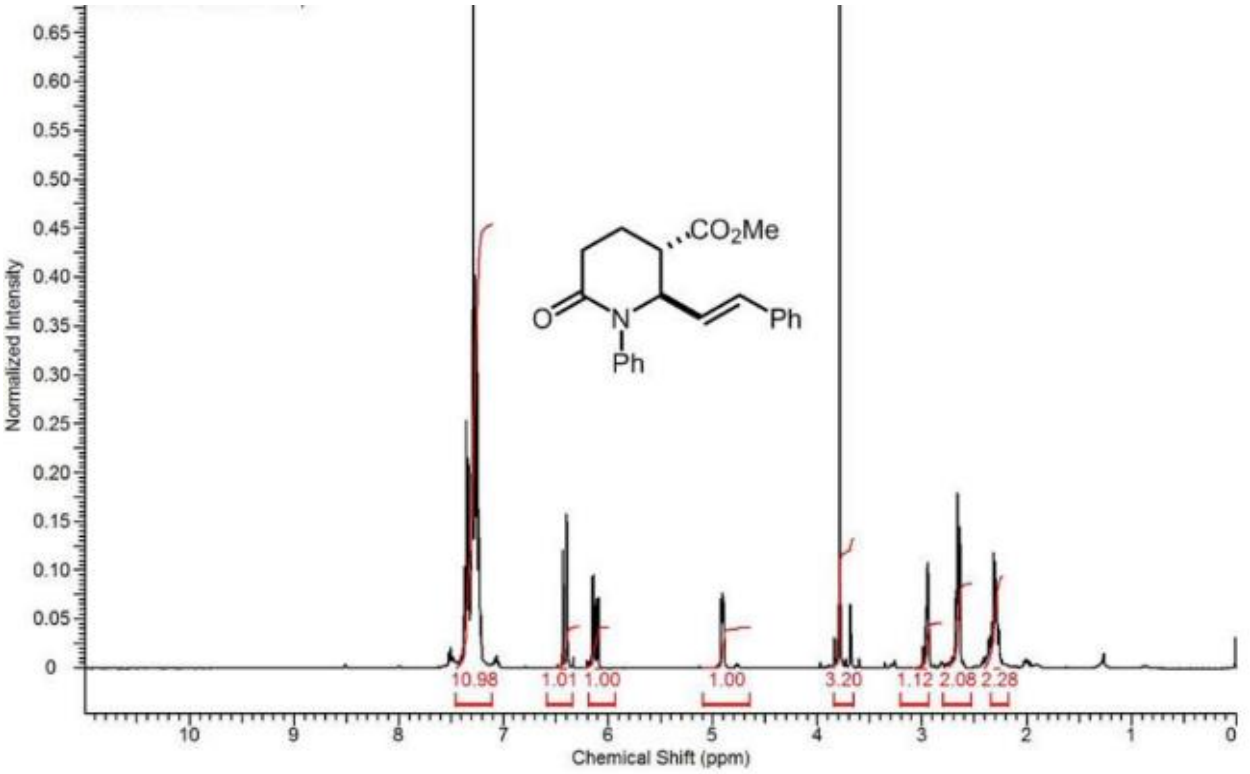
Spectrum 1-136: DEPT-135 spectrum of **6j2.**



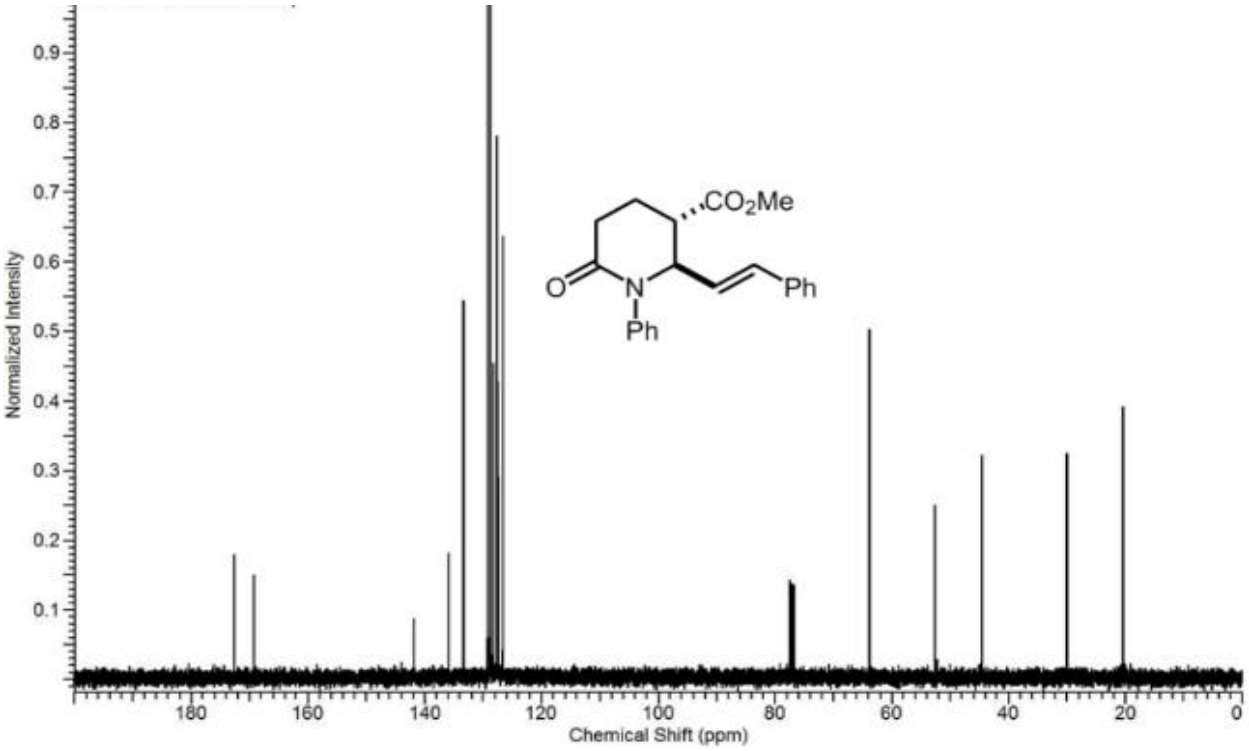
Spectrum 1-137: GC spectrum of **7a2.**



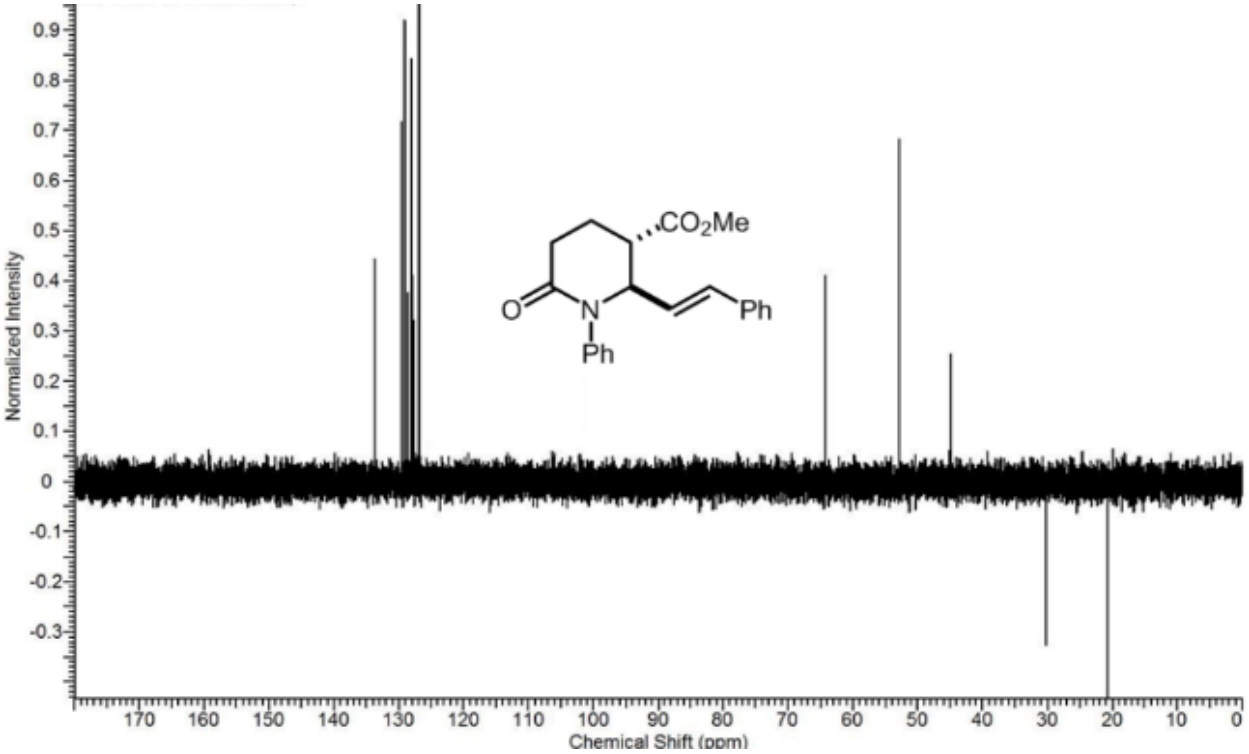
Spectrum 1-138: MS spectrum of **7a2.**



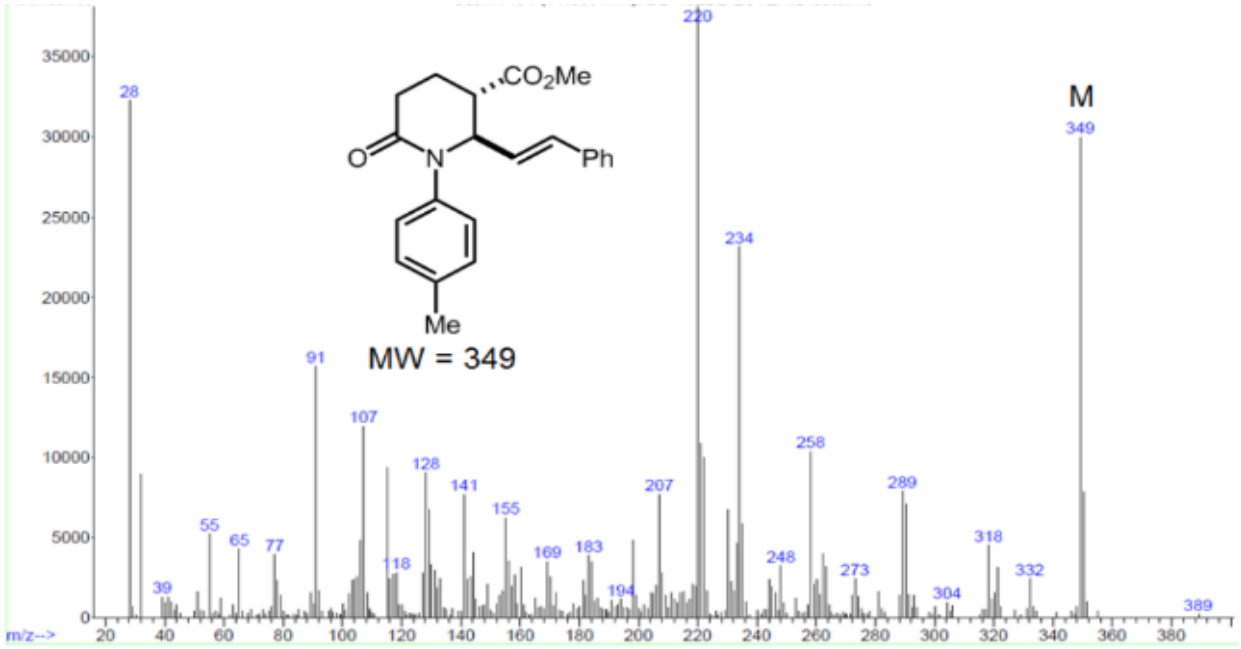
Spectrum 1-139: ^{1}H NMR spectrum of **7a2.**



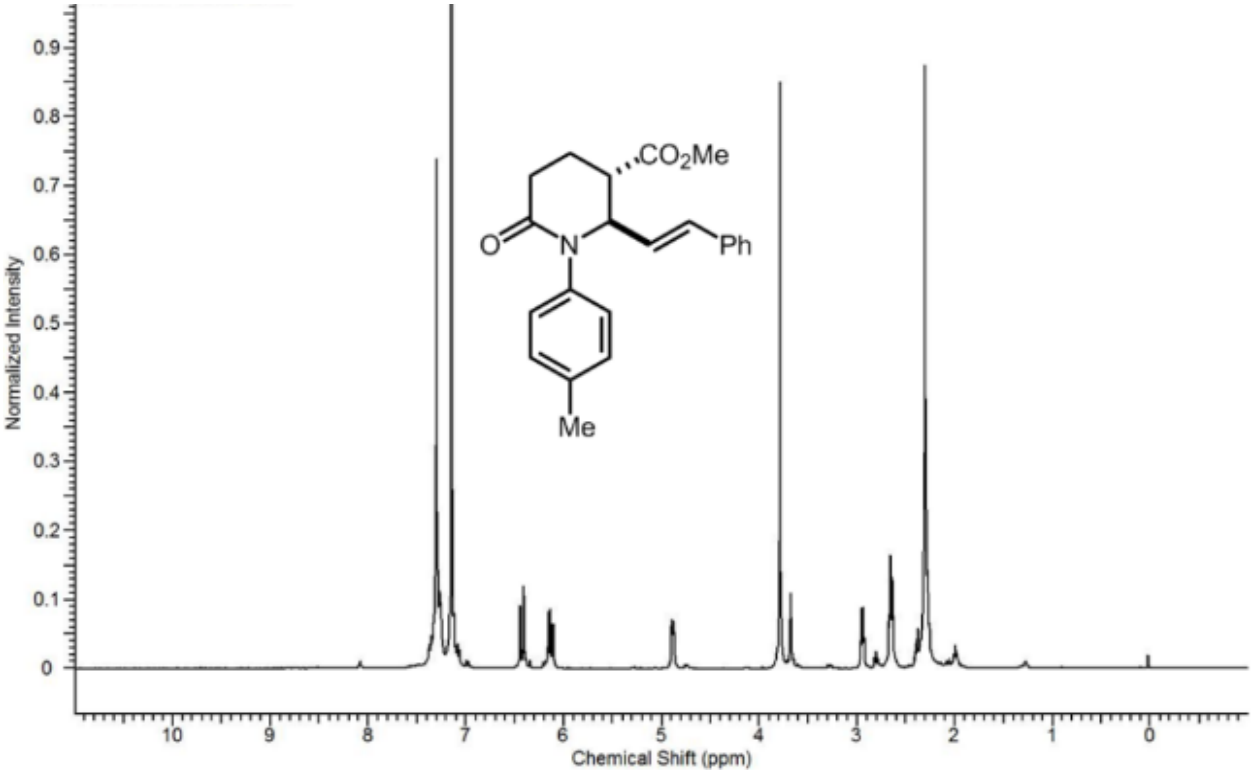
Spectrum 1-140: ^{13}C NMR spectrum of **7a2.**



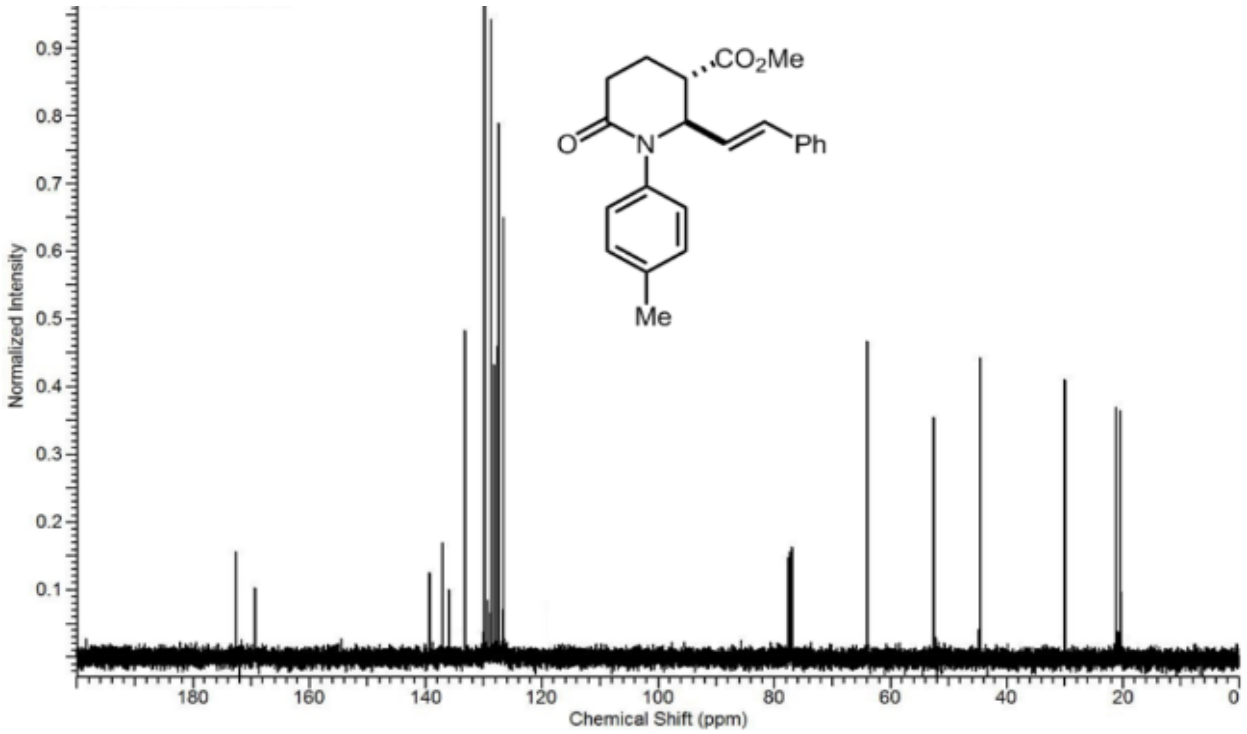
Spectrum 1-141: DEPT-135 spectrum of **7a2.**



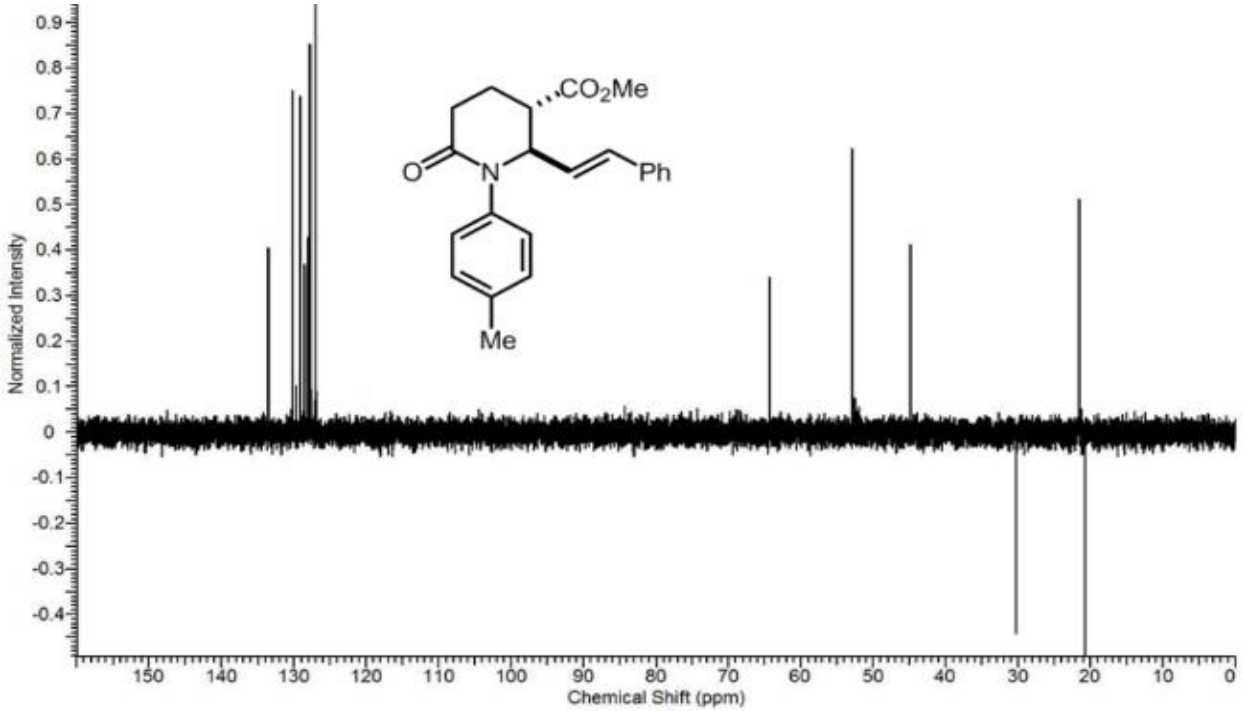
Spectrum 1-**142**: MS spectrum of **7b2.**



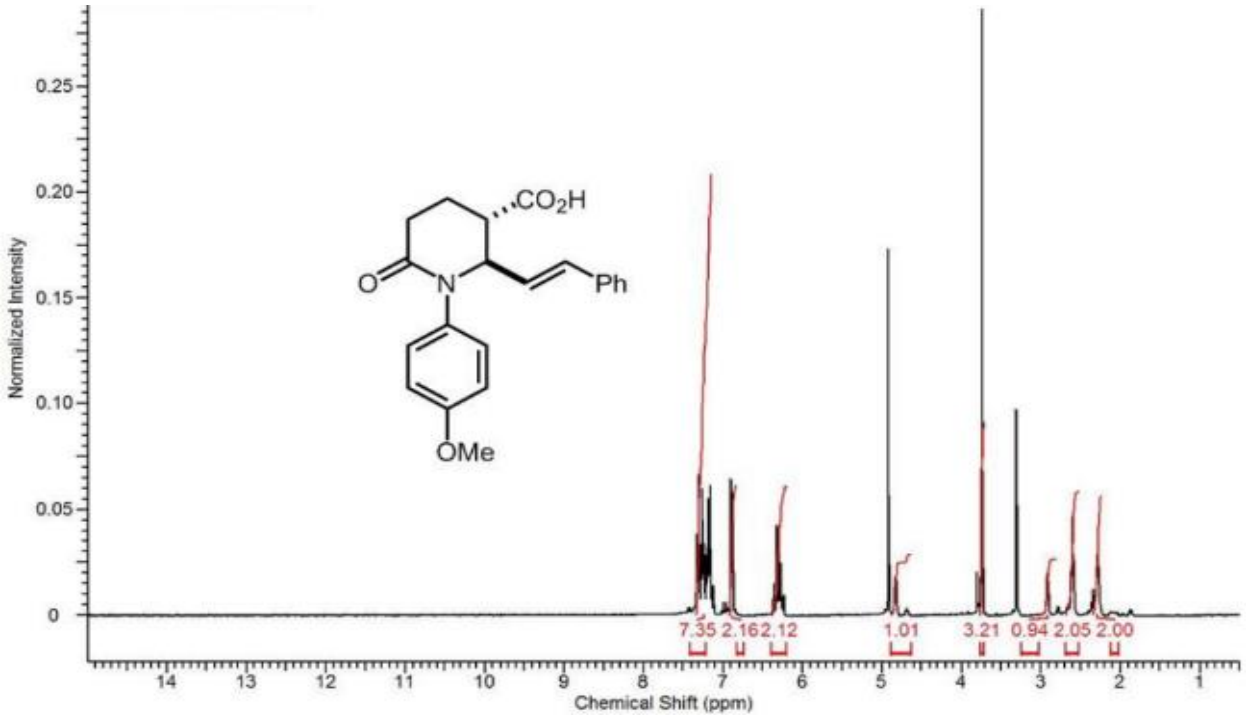
Spectrum 1-**143**: ^{1}H NMR spectrum of **7b2.**



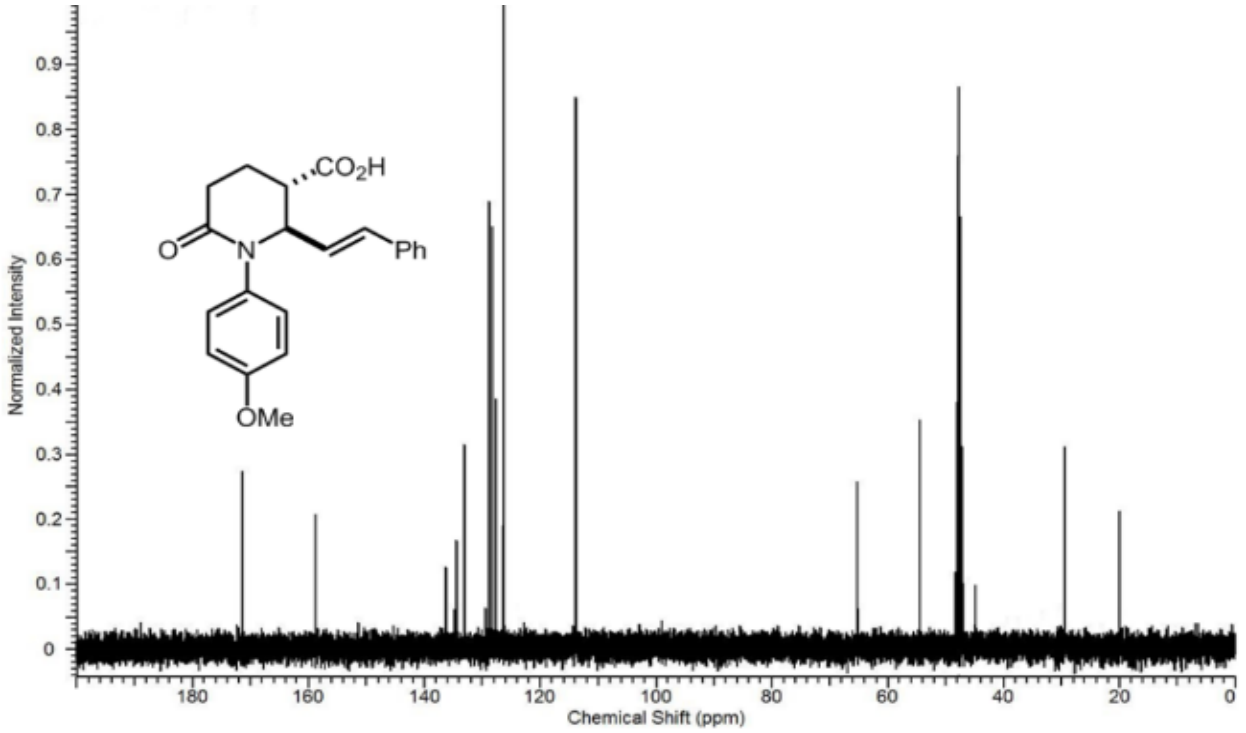
Spectrum 1-**144**: ^{13}C NMR spectrum of **7b2.**



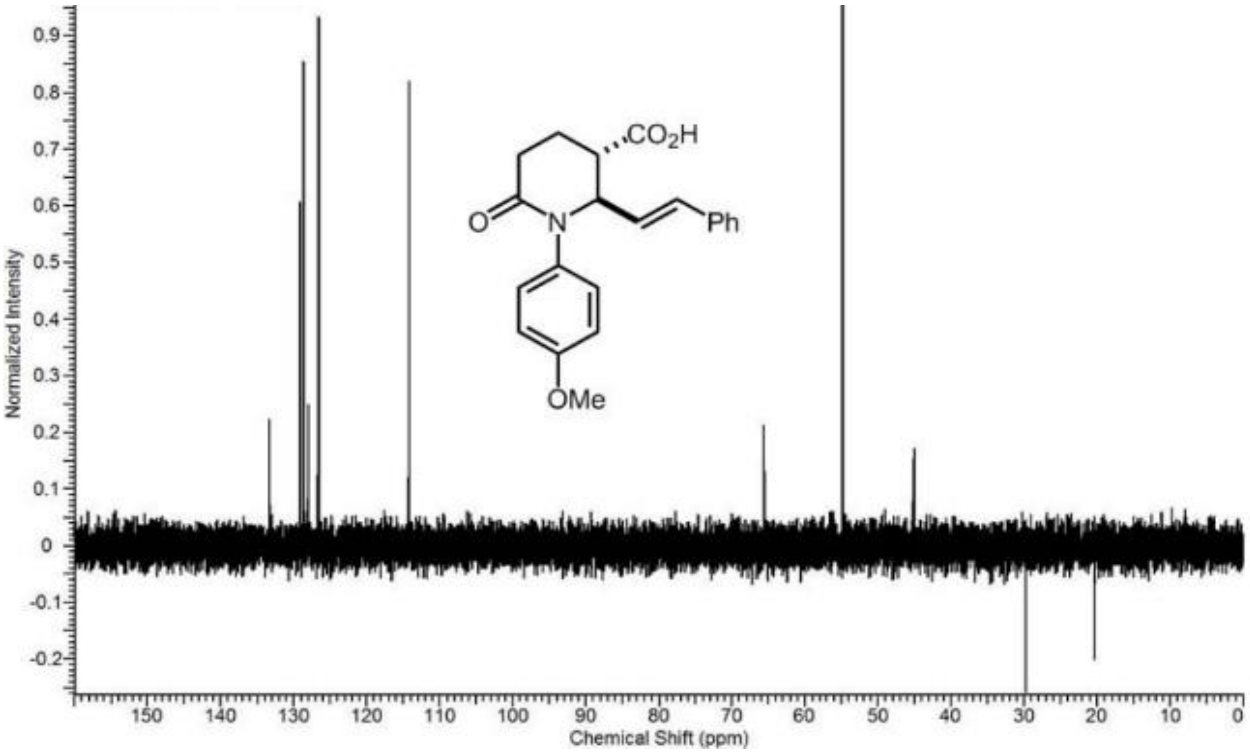
Spectrum 1-**155**: DEPT-135 NMR spectrum of **7b2.**



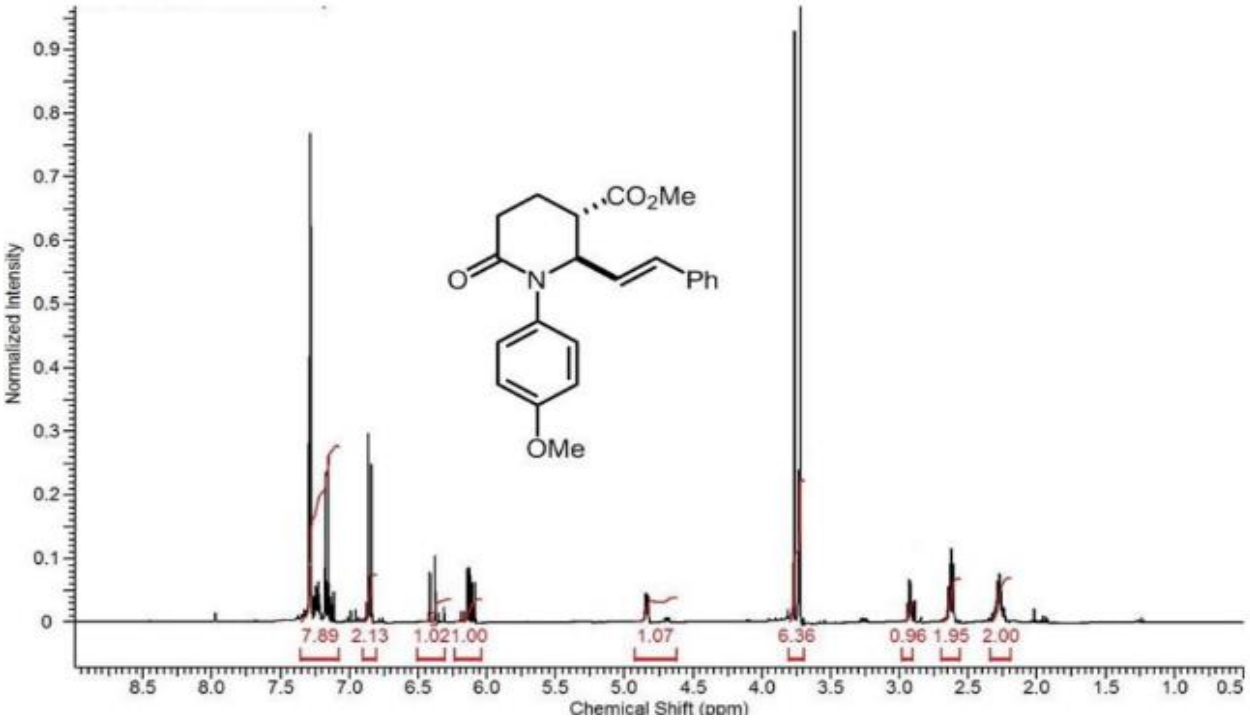
Spectrum 1-**146**: ^{1}H NMR spectrum of **7c1.**



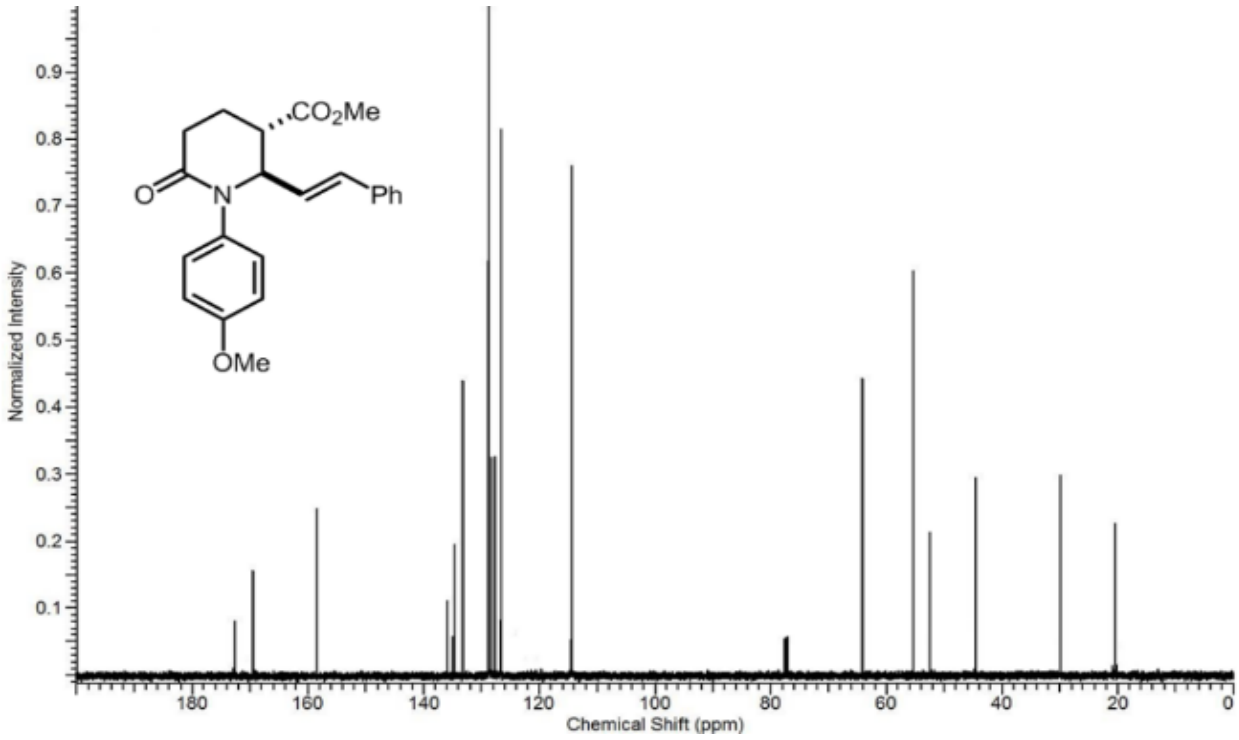
Spectrum 1-**147**: ^{13}C NMR spectrum of **7c1.**



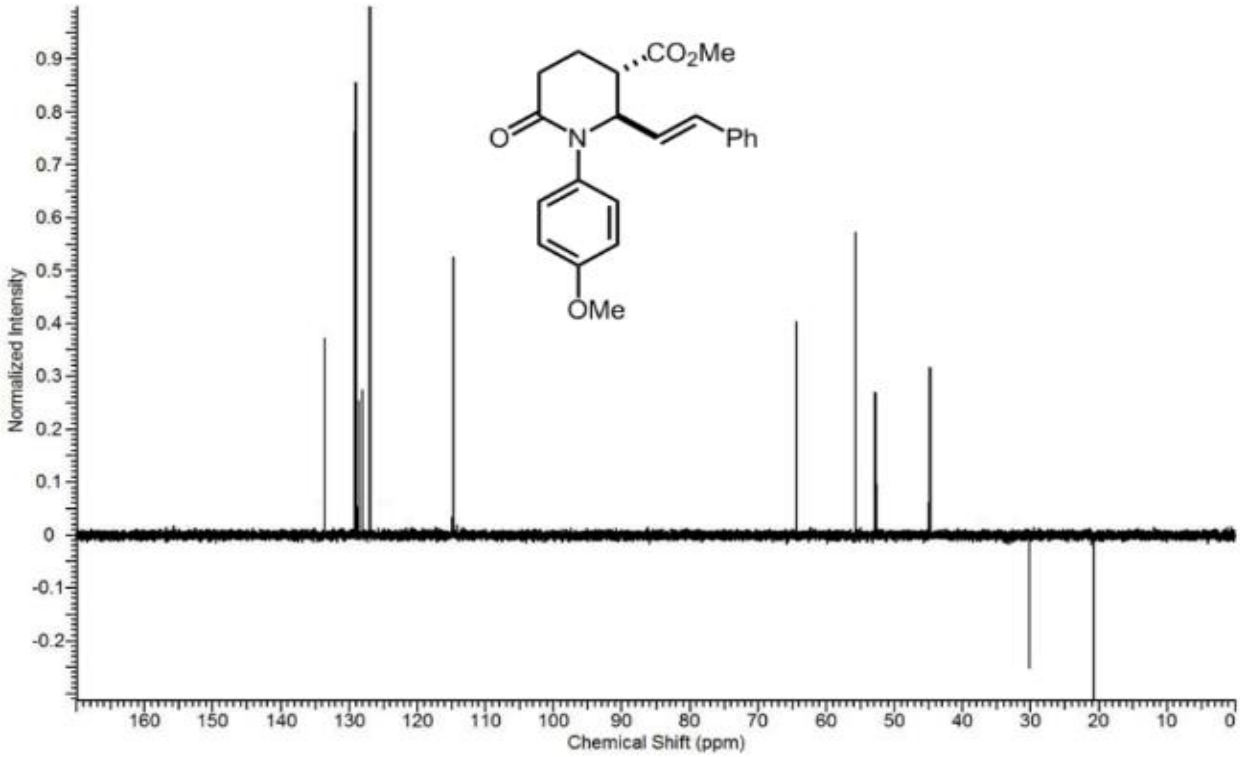
Spectrum 1-**148**: DEPT-135 NMR spectrum of **7c1.**



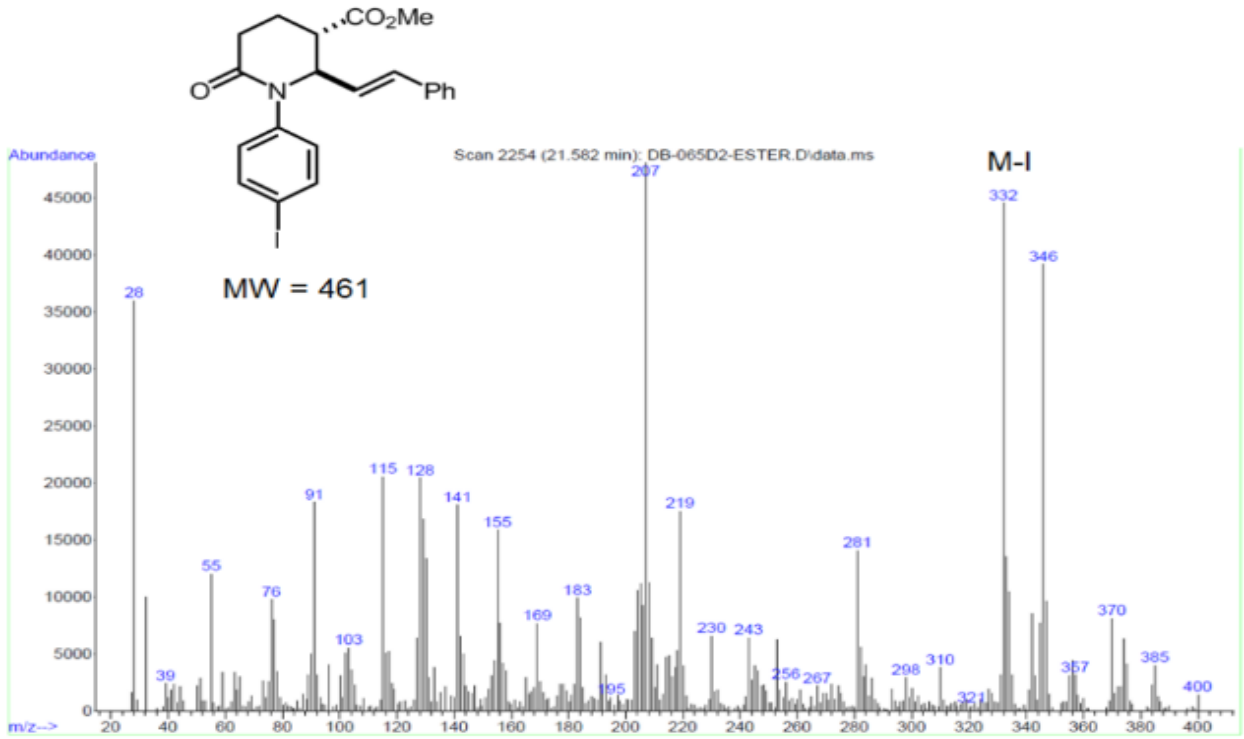
Spectrum 1-**149**: ^{1}H NMR spectrum of **7c2.**



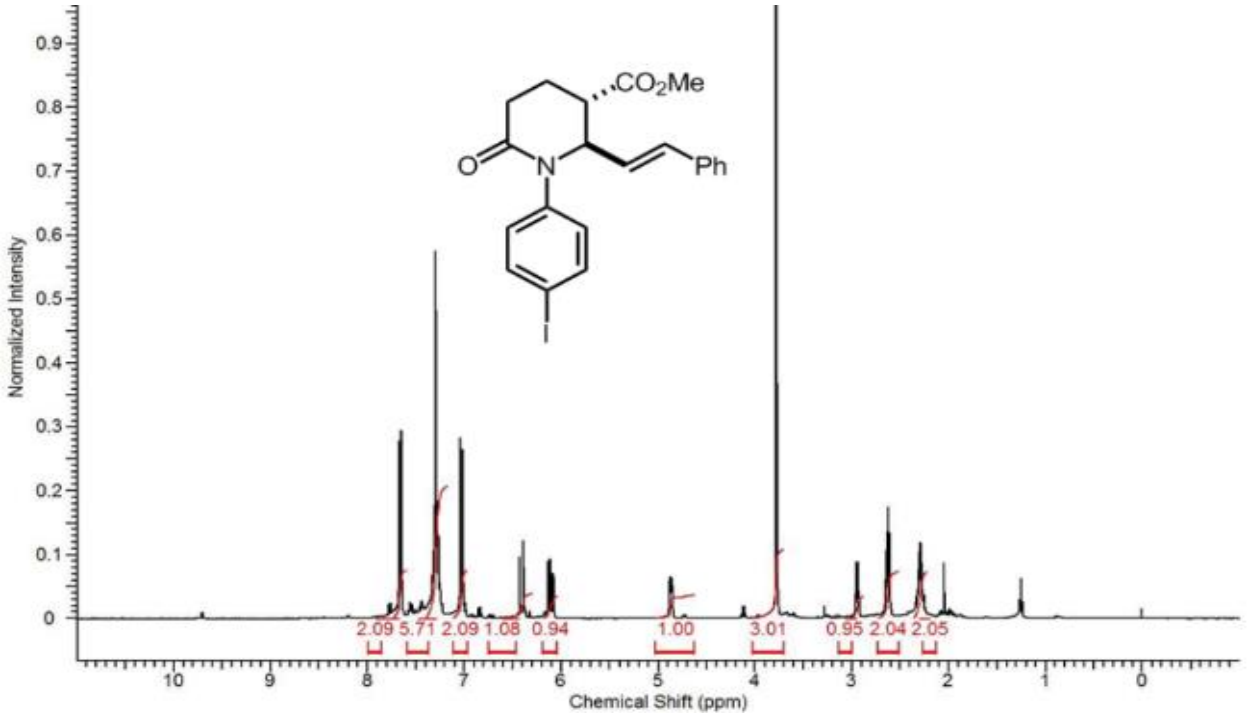
Spectrum 1-**150**: ^{13}C NMR spectrum of **7c2.**



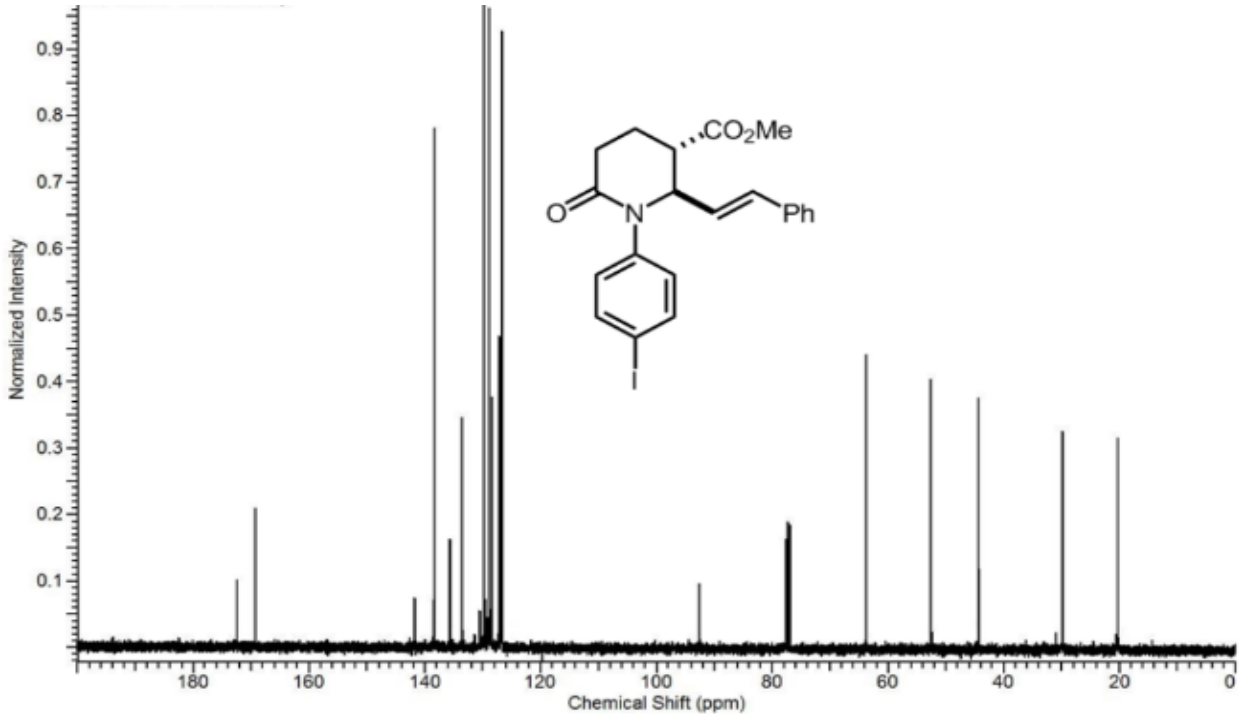
Spectrum 1-**151**: DEPT-135 NMR spectrum of **7c2.**



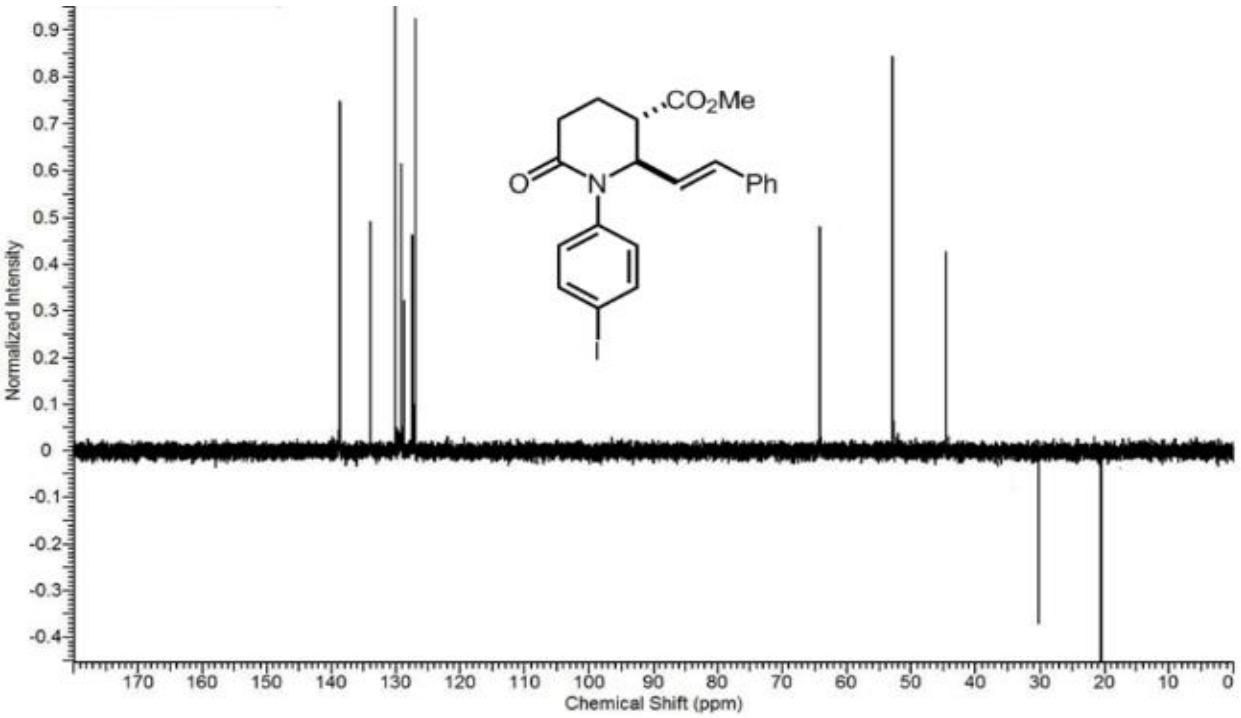
Spectrum 1-**152**: MS spectrum of **7d2.**



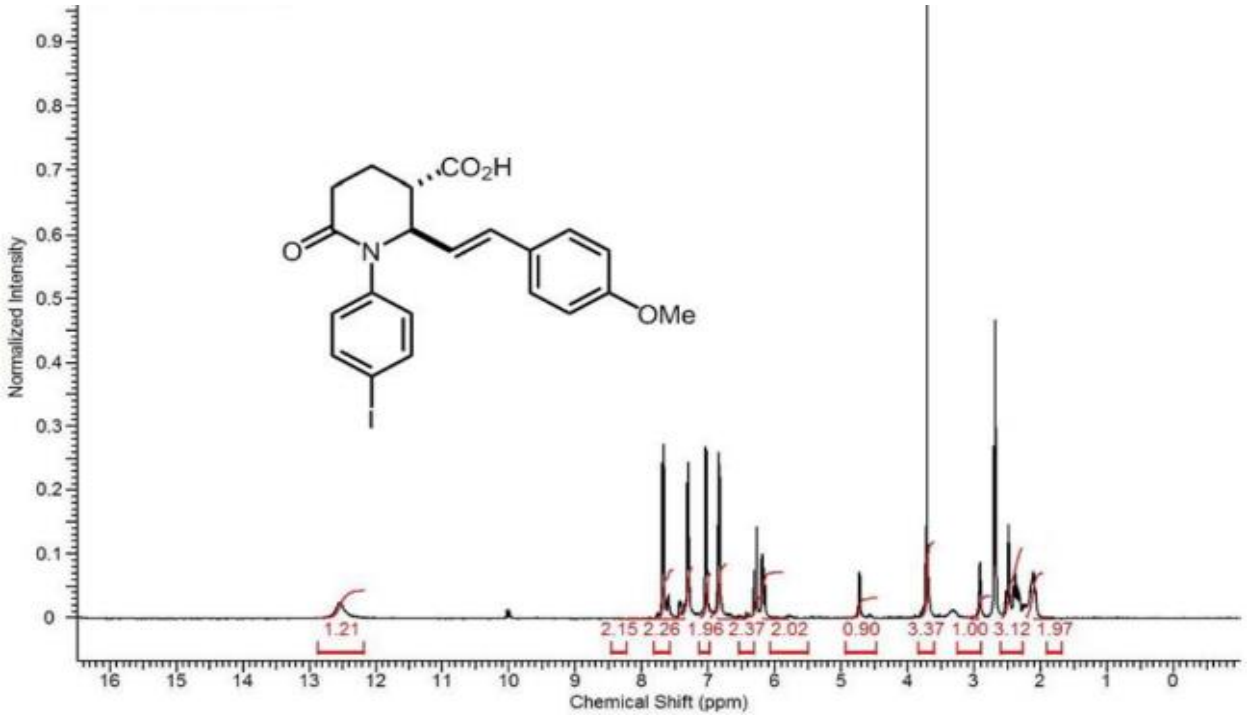
Spectrum 1-**153**: ^{1}H NMR spectrum of **7d2.**



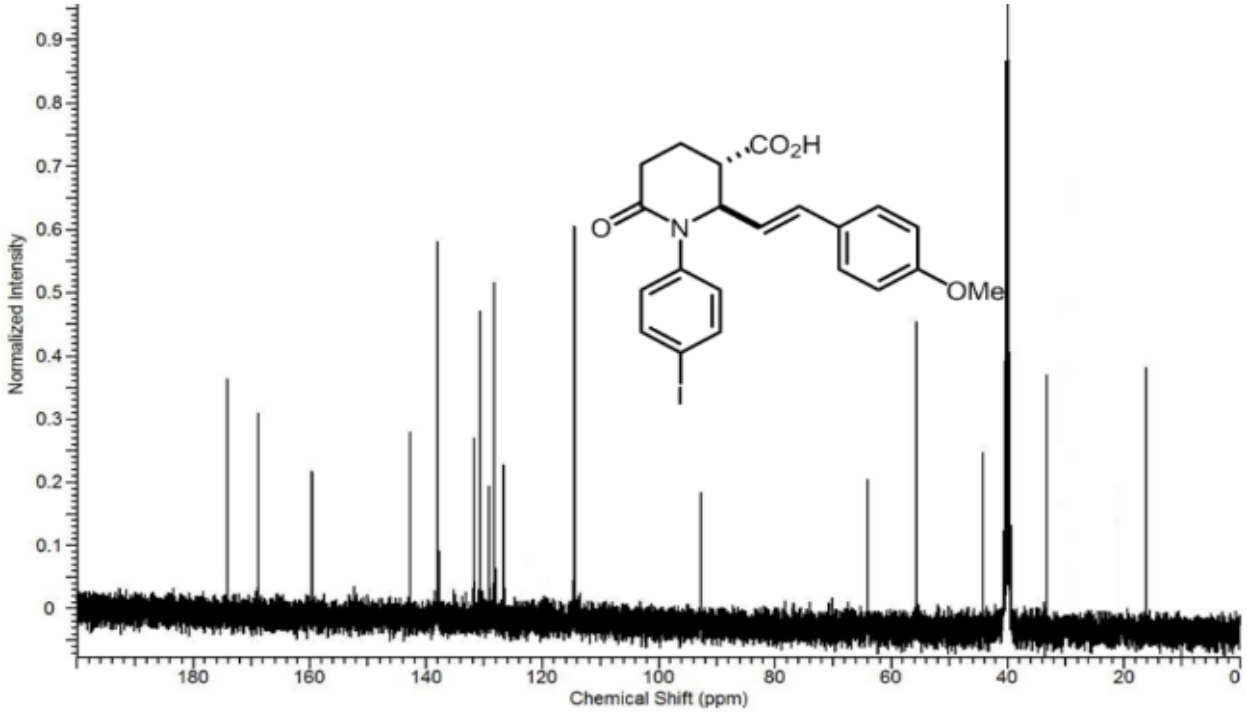
Spectrum 1-**154**: ^{13}C NMR spectrum of **7d2.**



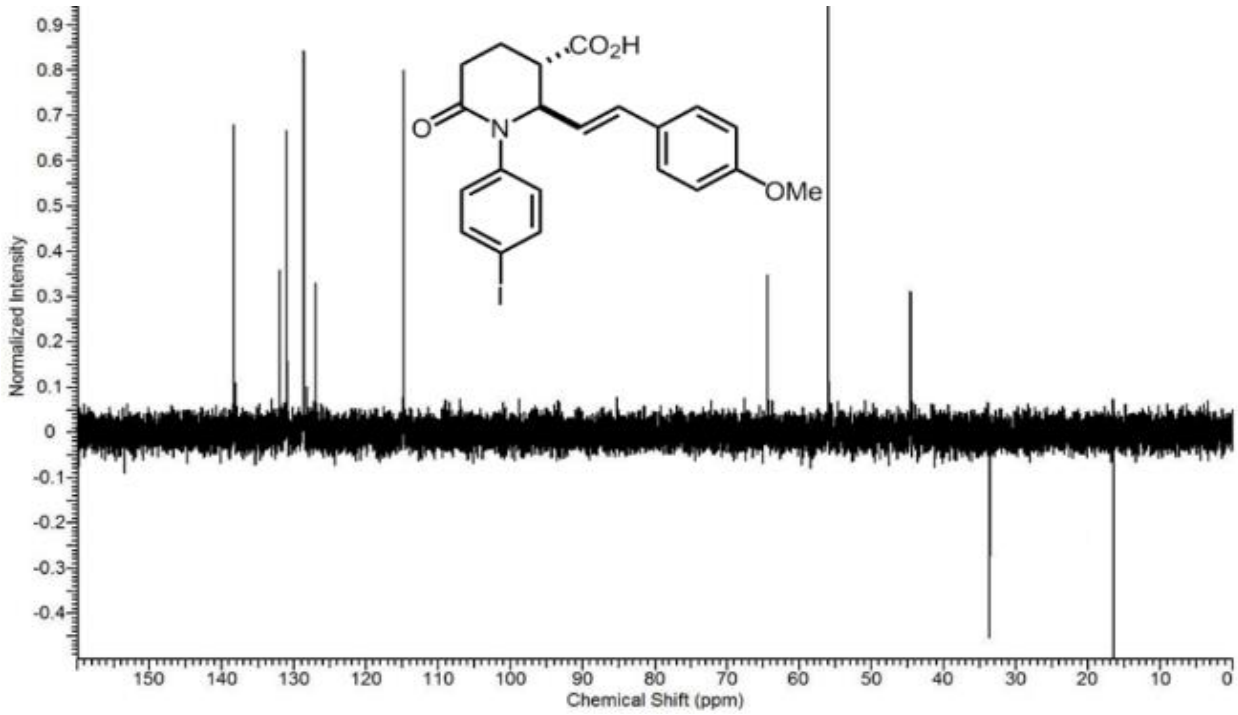
Spectrum 1-**155**: DEPT-135 NMR spectrum of **7d2.**



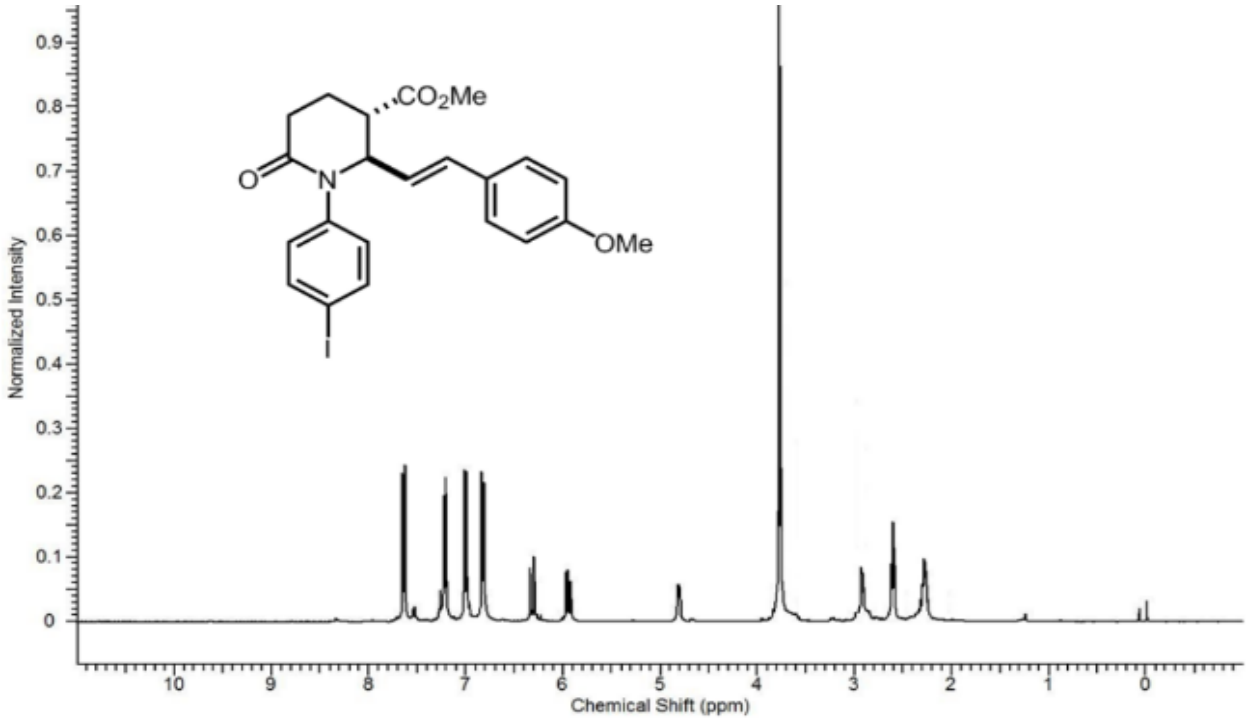
Spectrum 1-**156**: ^{1}H NMR spectrum of **7e1.**



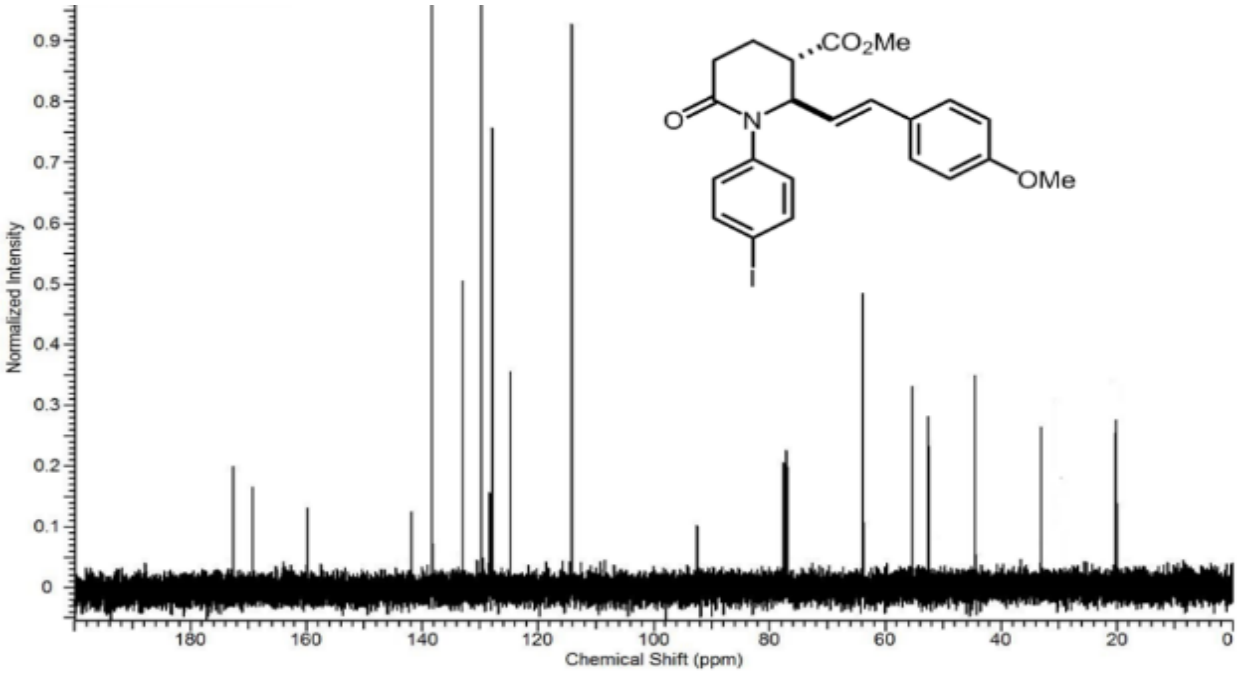
Spectrum 1-**157**: ^{13}C NMR spectrum of **7e1.**



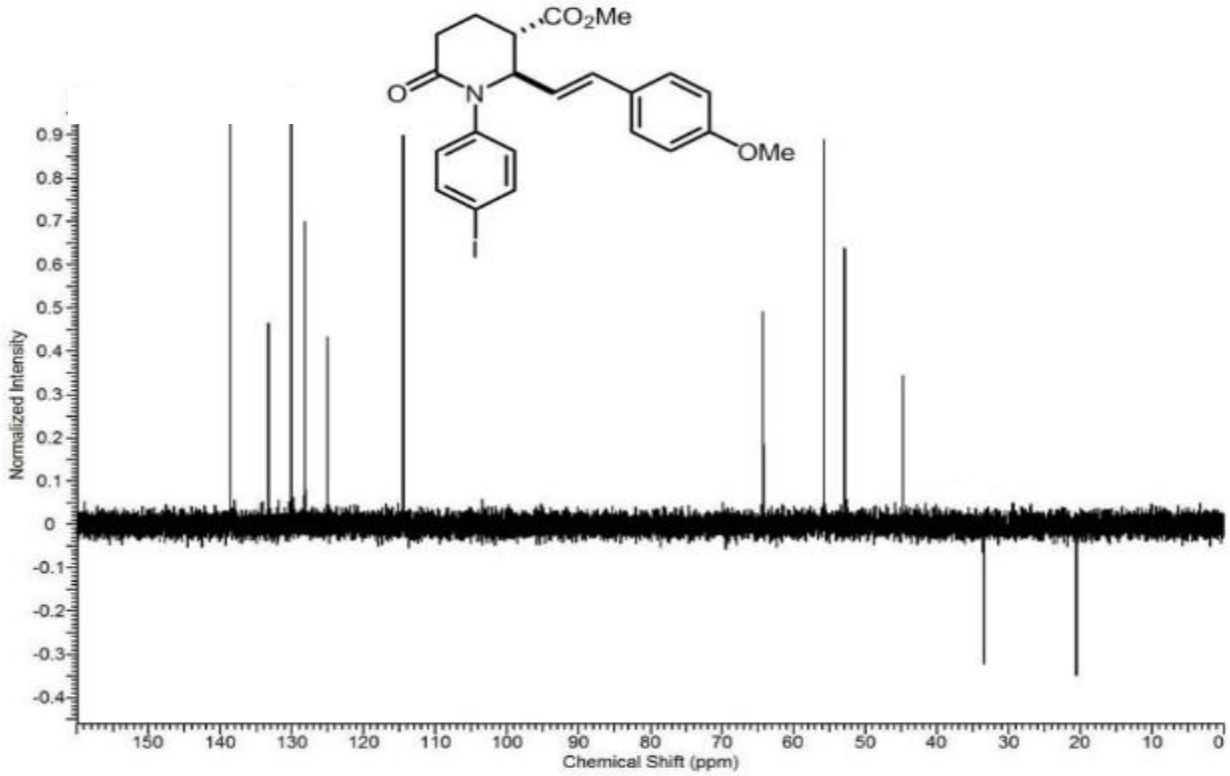
Spectrum 1-**158**: DEPT-135 NMR spectrum of **7e1.**



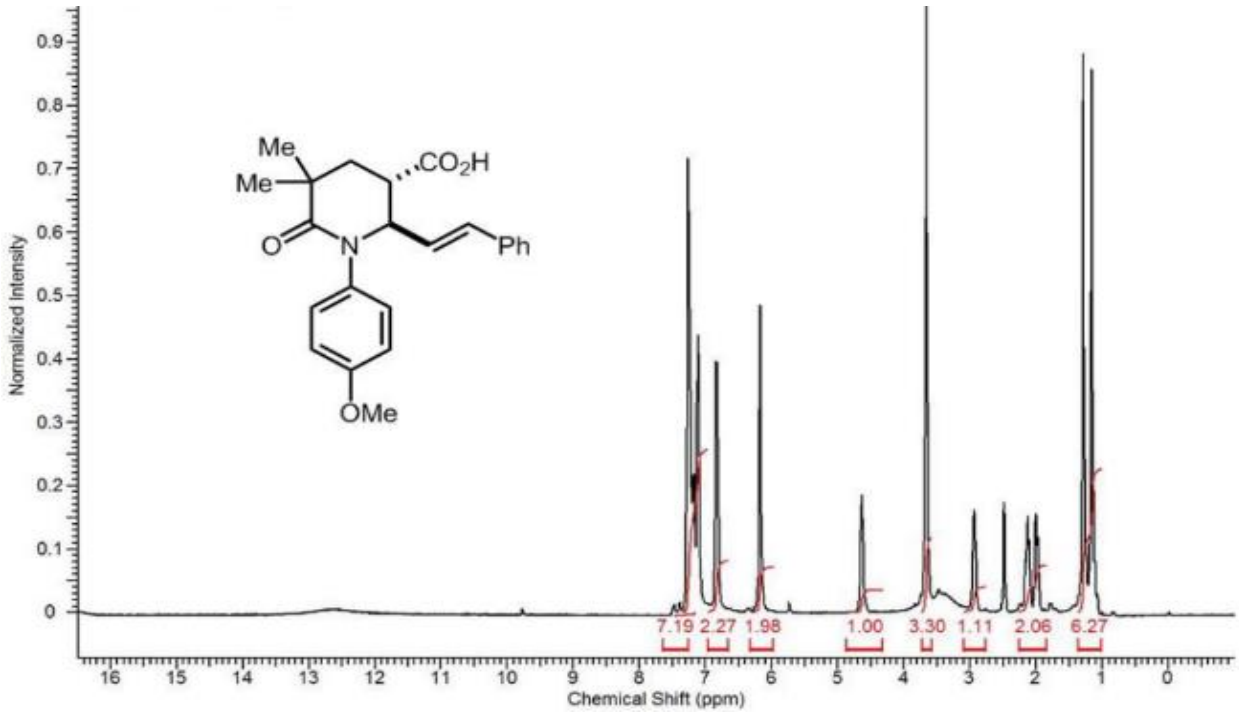
Spectrum 1-**159**: ^{1}H NMR spectrum of **7e2.**



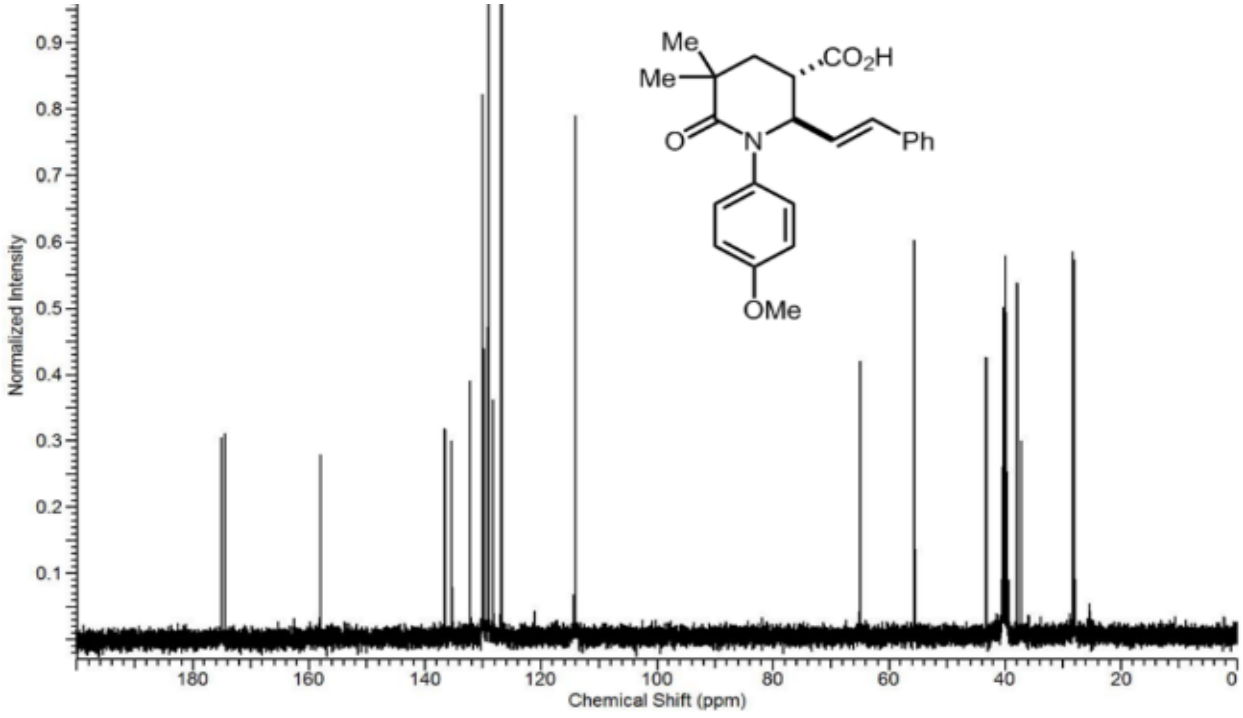
Spectrum 1-**160**: ^{13}C NMR spectrum of **7e2.**



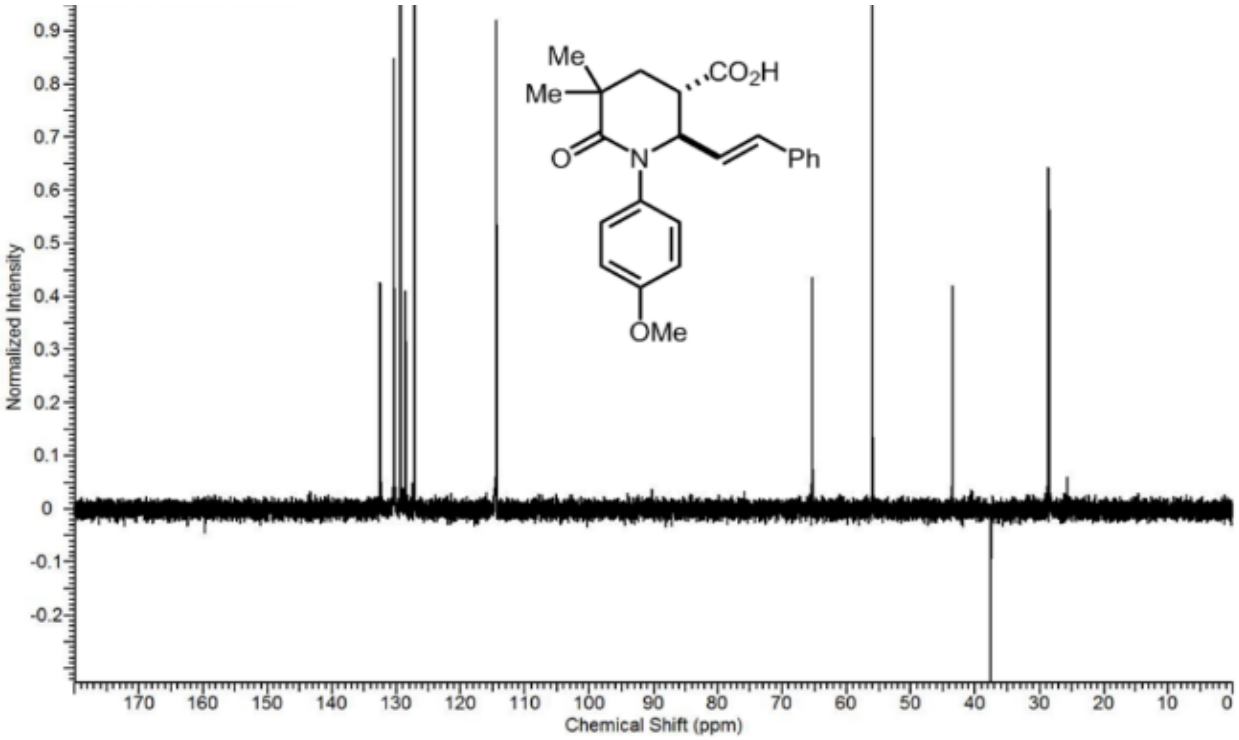
Spectrum 1-**161**: DEPT-135 NMR spectrum of **7e2.**



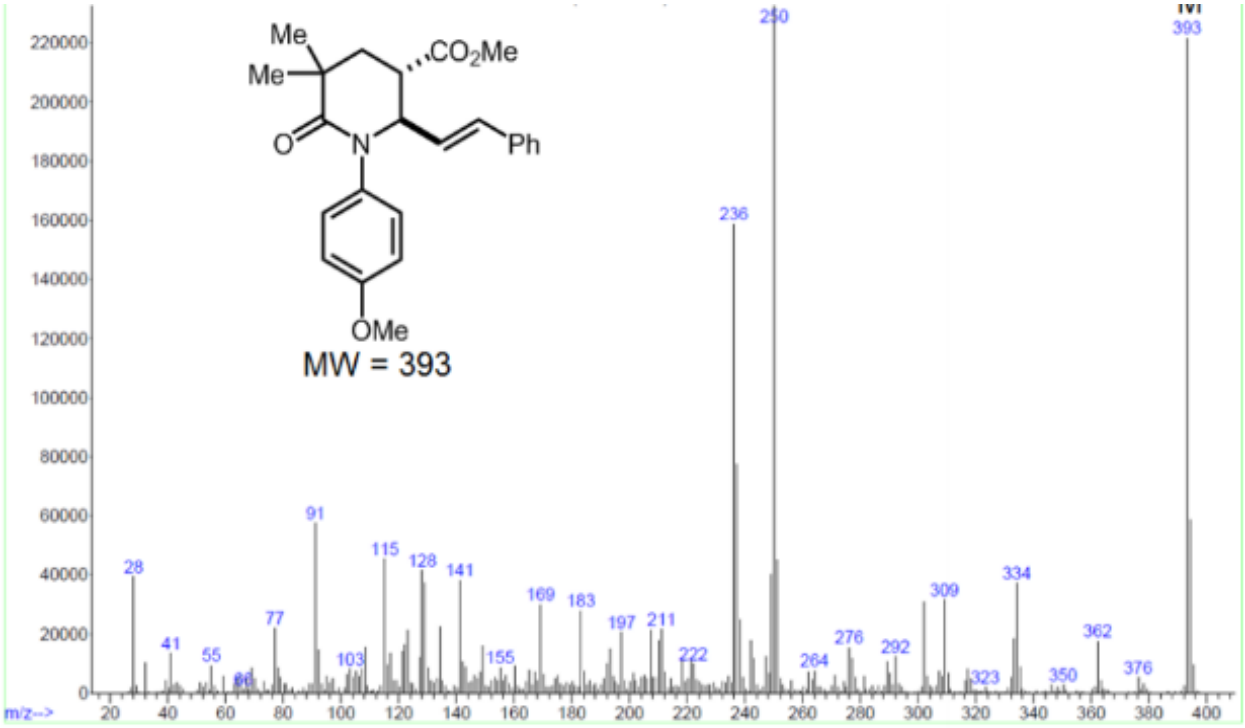
Spectrum 1-**162**: ^{1}H NMR spectrum of **7f1.**



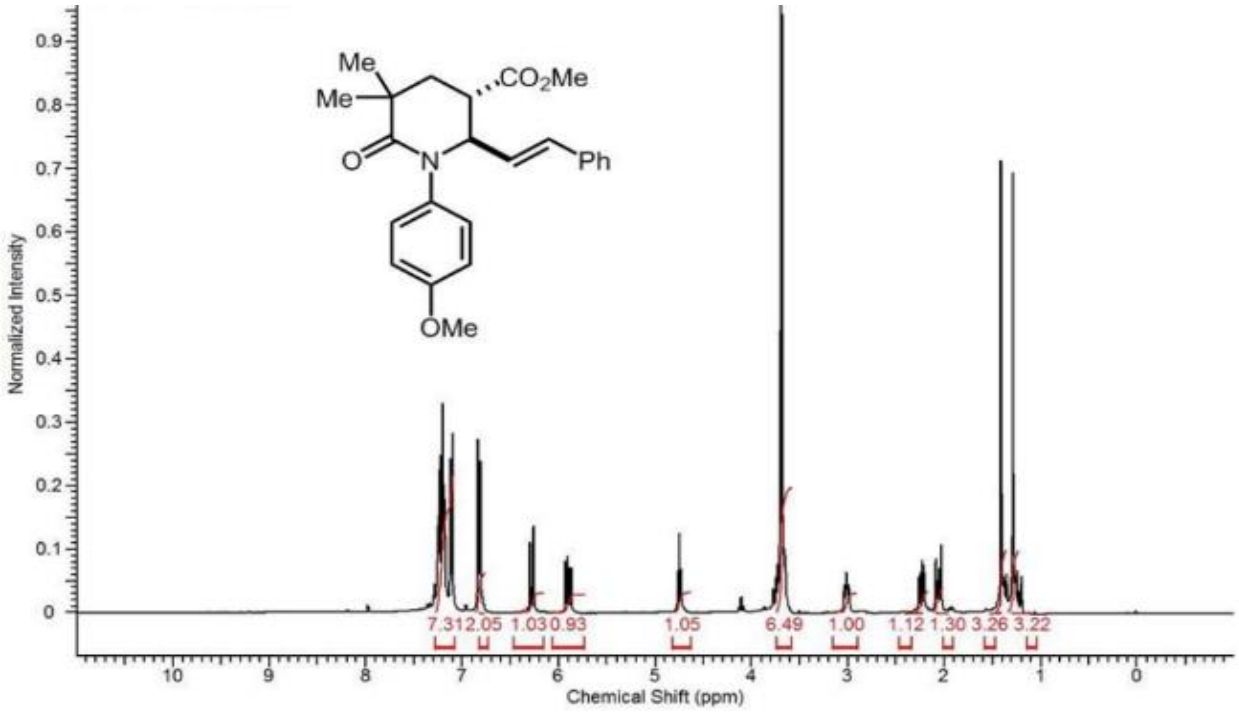
Spectrum 1-**173**: ^{13}C NMR spectrum of **7f1.**



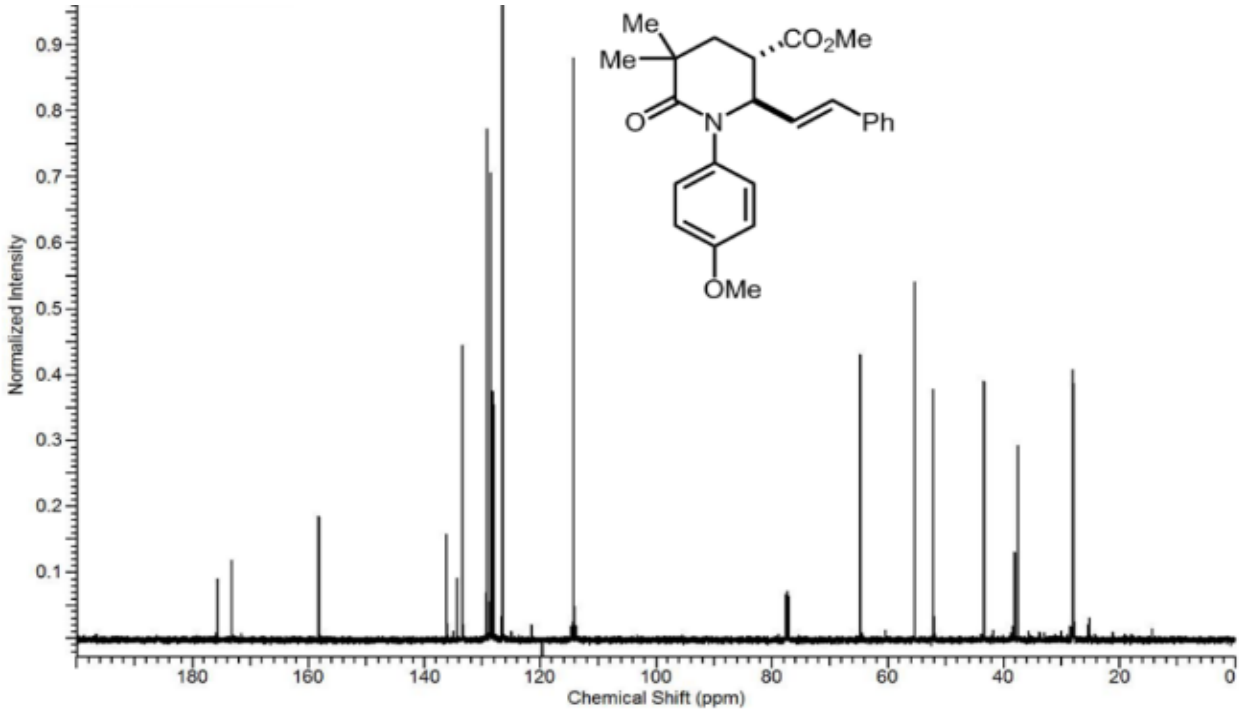
Spectrum 1-**174**: DEPT-135 NMR spectrum of **7f1.**



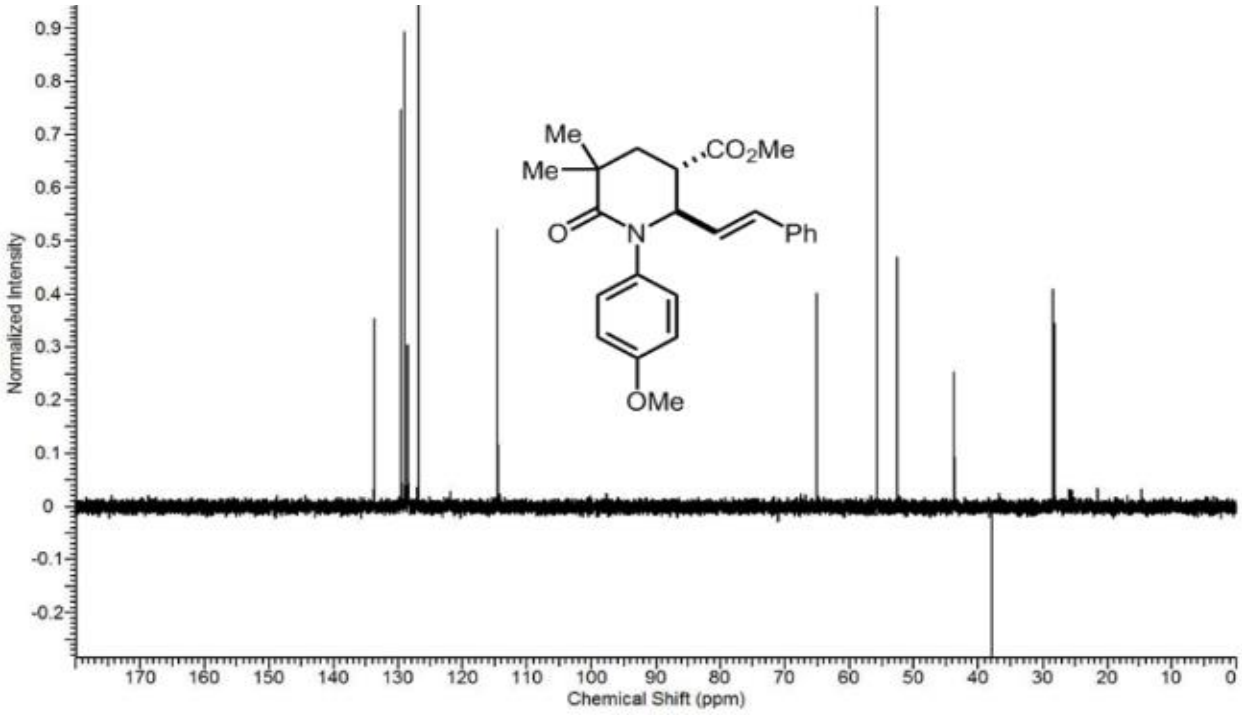
Spectrum 1-**175**: MS spectrum of 7**f2.**



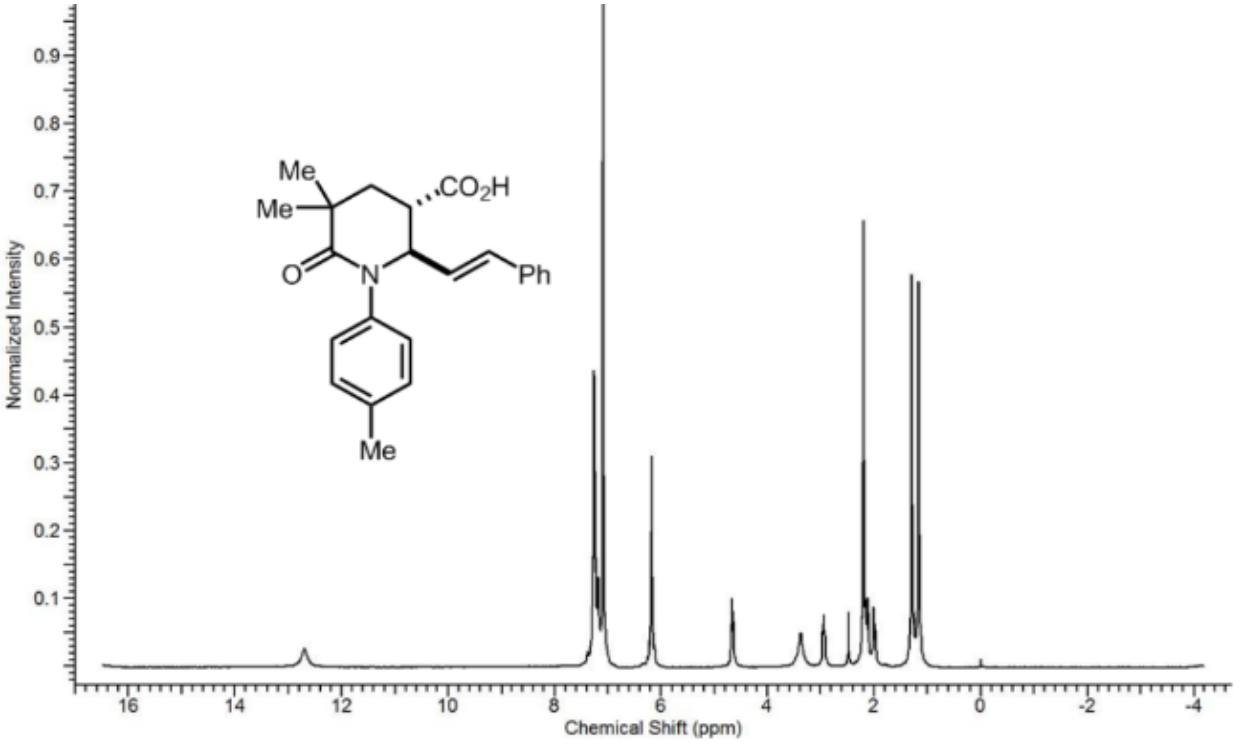
Spectrum 1-**176**: ^{1}H NMR spectrum of **7f2.**



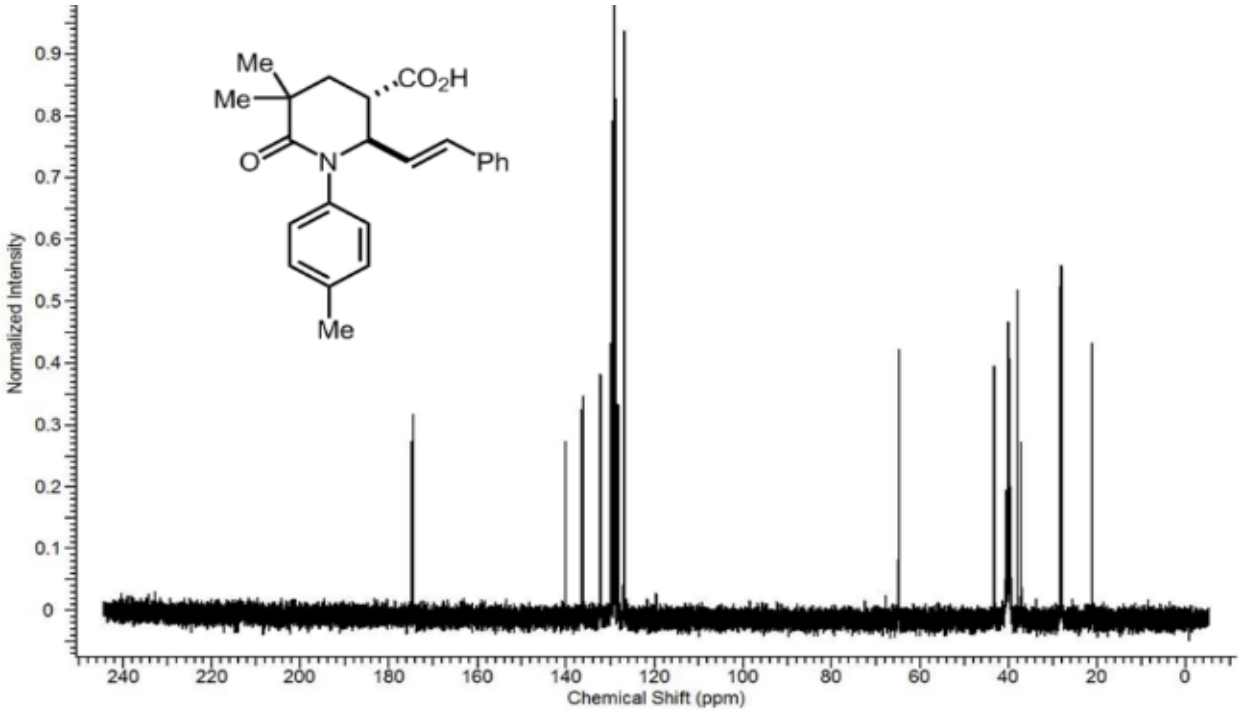
Spectrum 1-**177**: ^{13}C NMR spectrum of **7f2.**



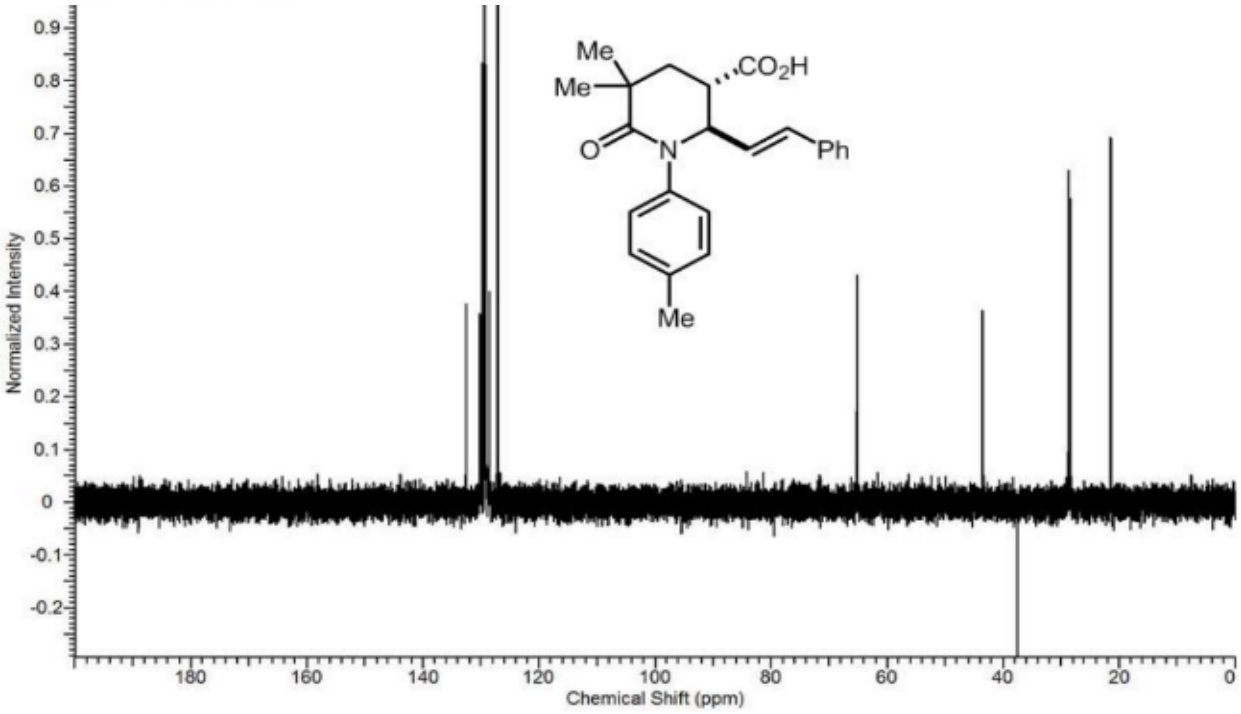
Spectrum 1-**178**: DEPT-135 NMR spectrum of **7f2.**



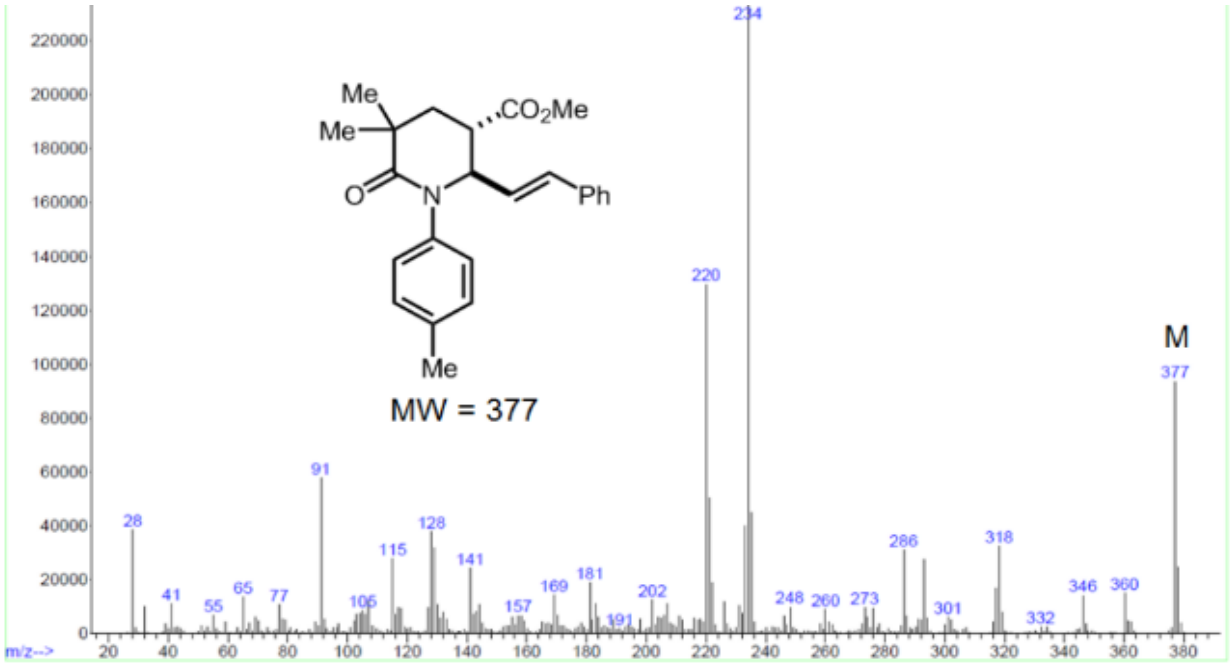
Spectrum 1-**179**: ^{1}H NMR spectrum of 7**g1.**



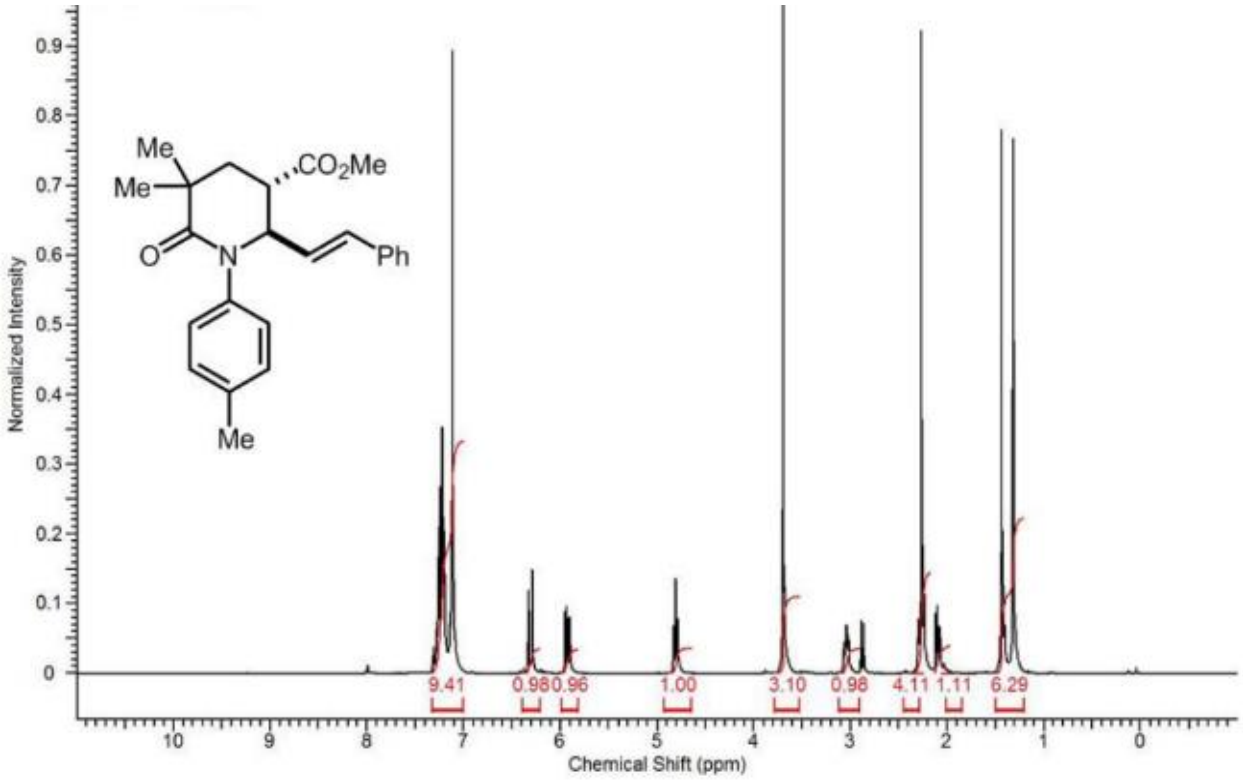
Spectrum 1-**180**: ^{13}C NMR spectrum of **7g1.**



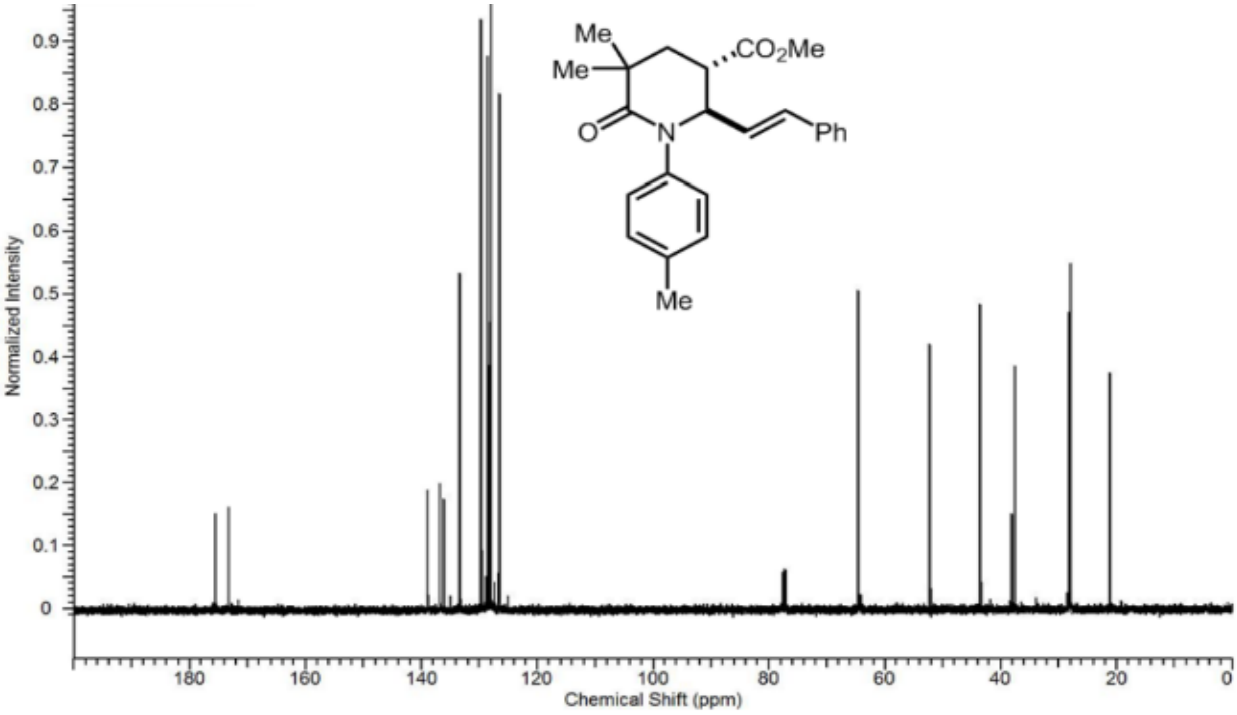
Spectrum 1-**171**: DEPT-135 NMR spectrum of **7g1.**



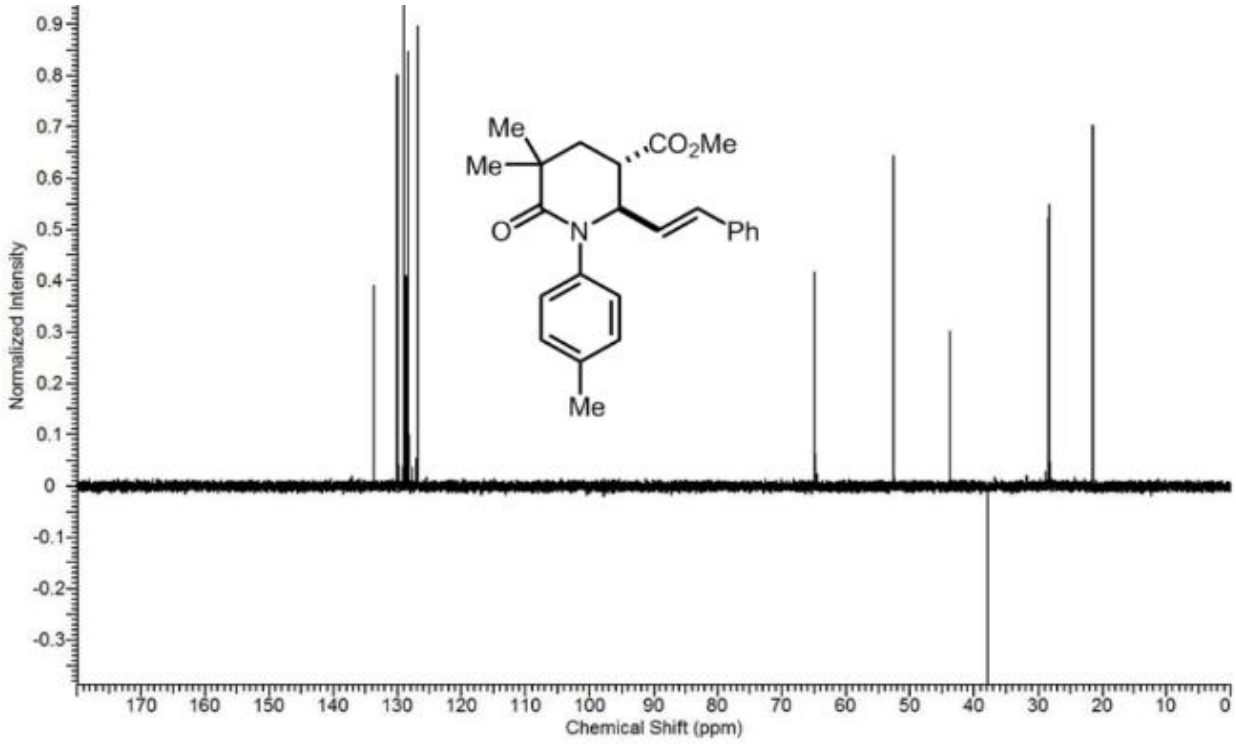
Spectrum 1-**172**: MS spectrum of **7g2.**



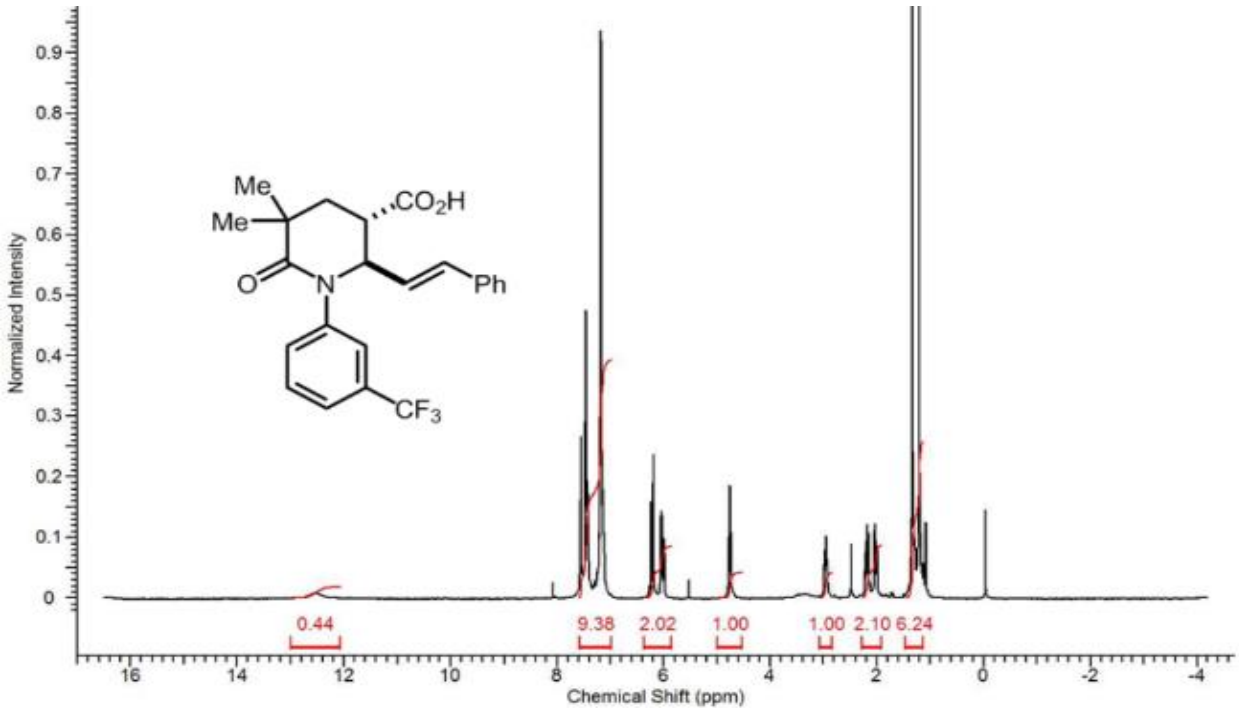
Spectrum 1-**173**: ^{1}H NMR spectrum of **7g2.**



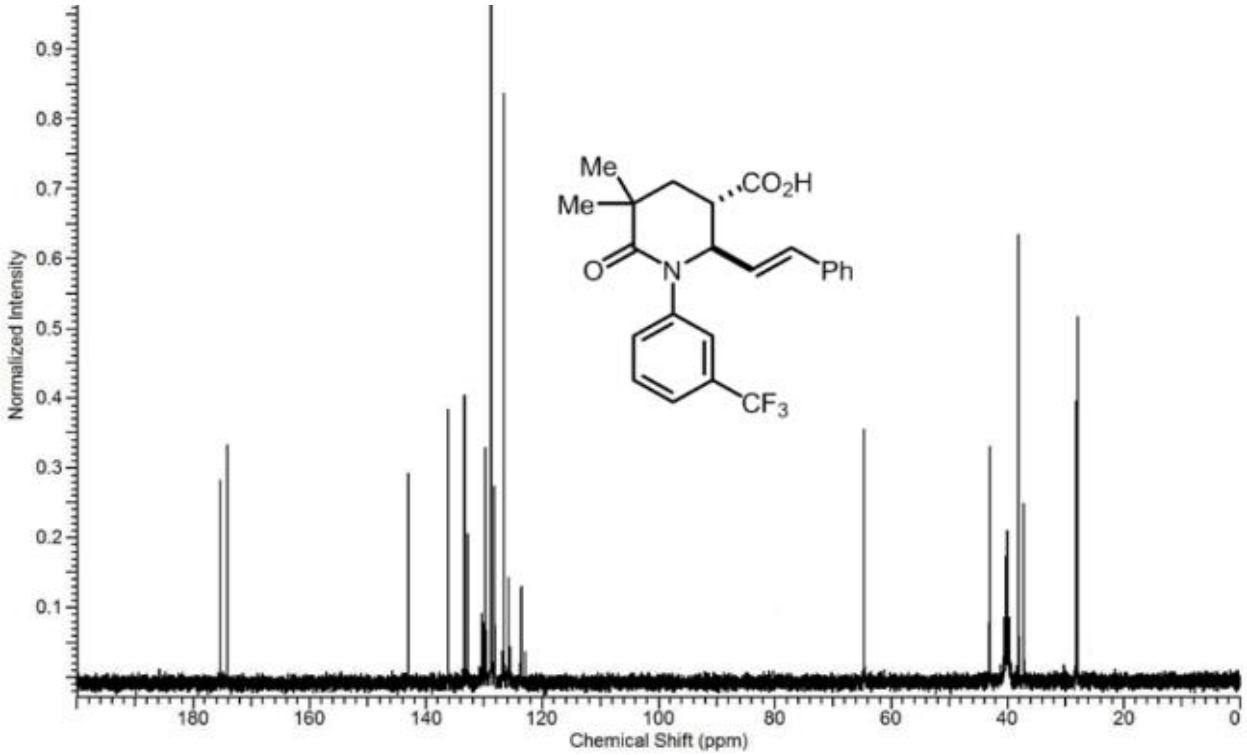
Spectrum 1-**174**: ^{13}C NMR spectrum of **7g2.**



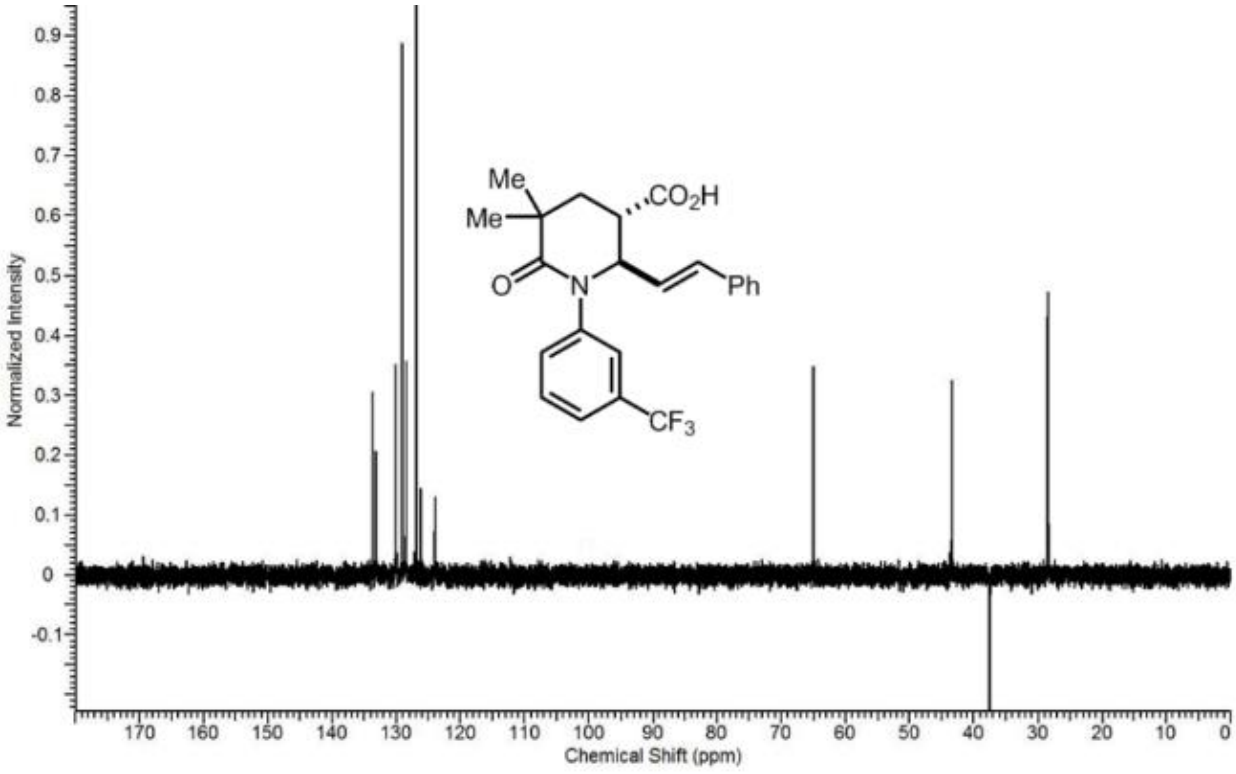
Spectrum 1-**175**: DEPT-135 NMR spectrum of **7g2.**



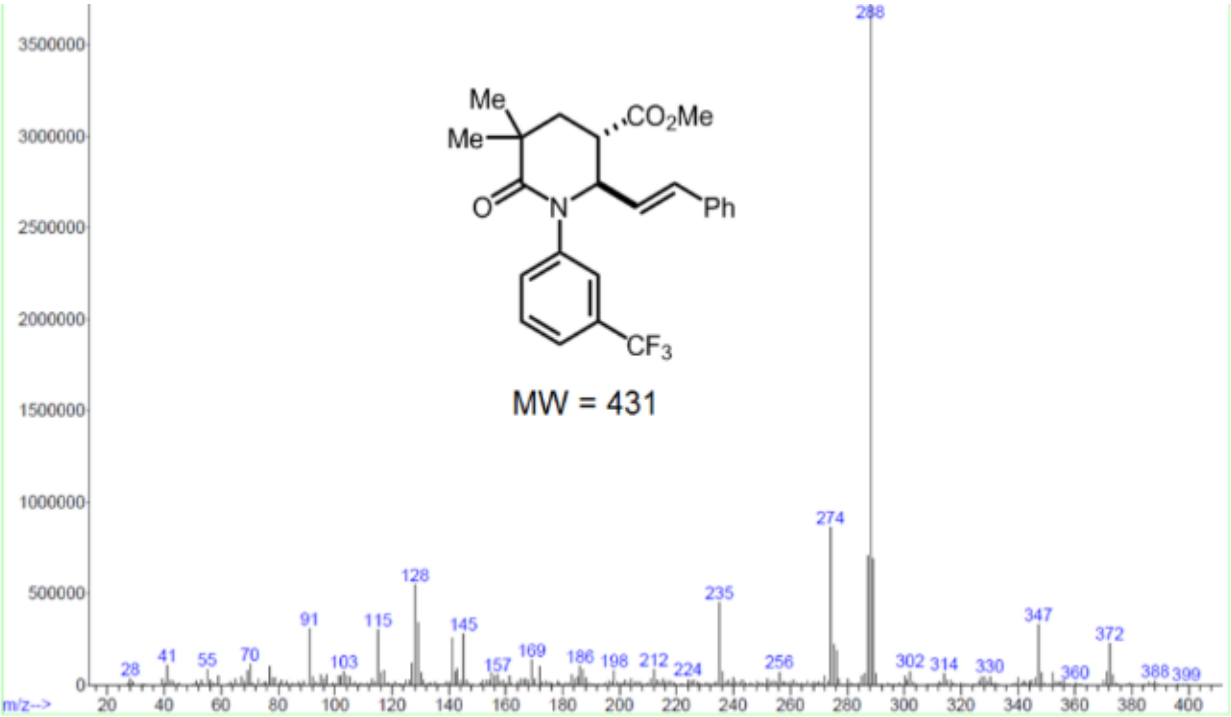
Spectrum 1-**176**: ^{1}H NMR spectrum of **71H.**



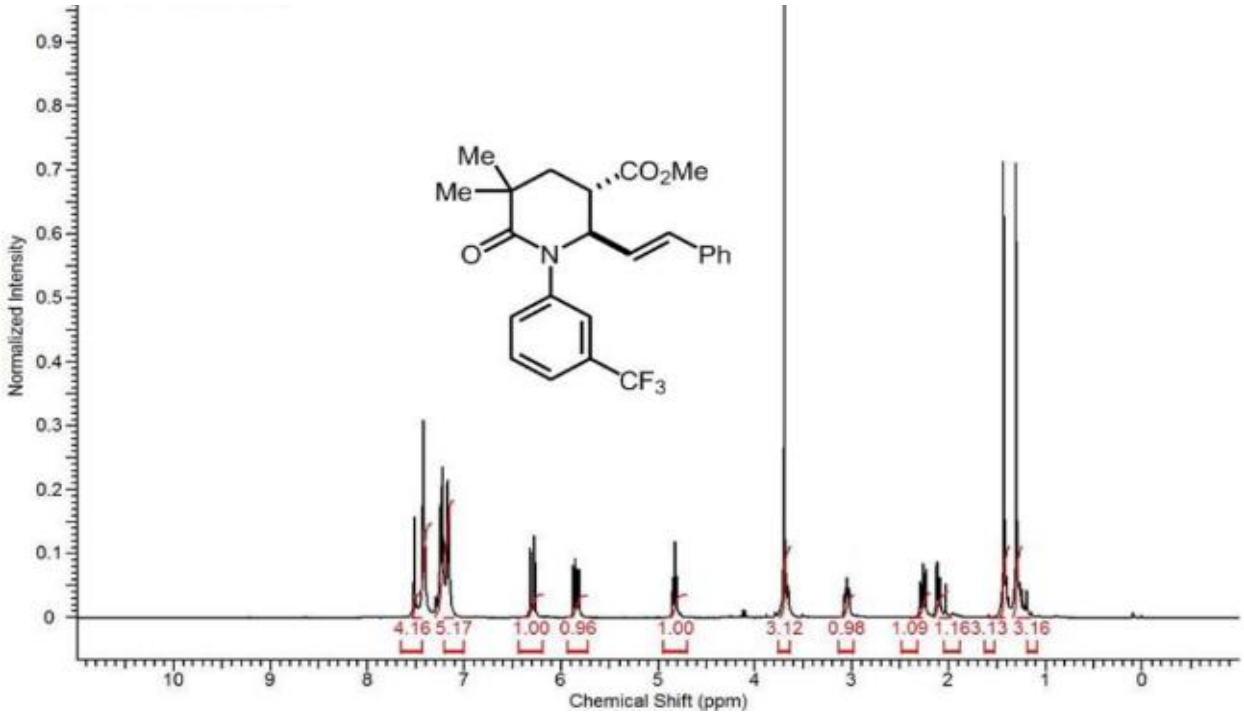
Spectrum 1-**177**: ^{13}C NMR spectrum of **71H.**



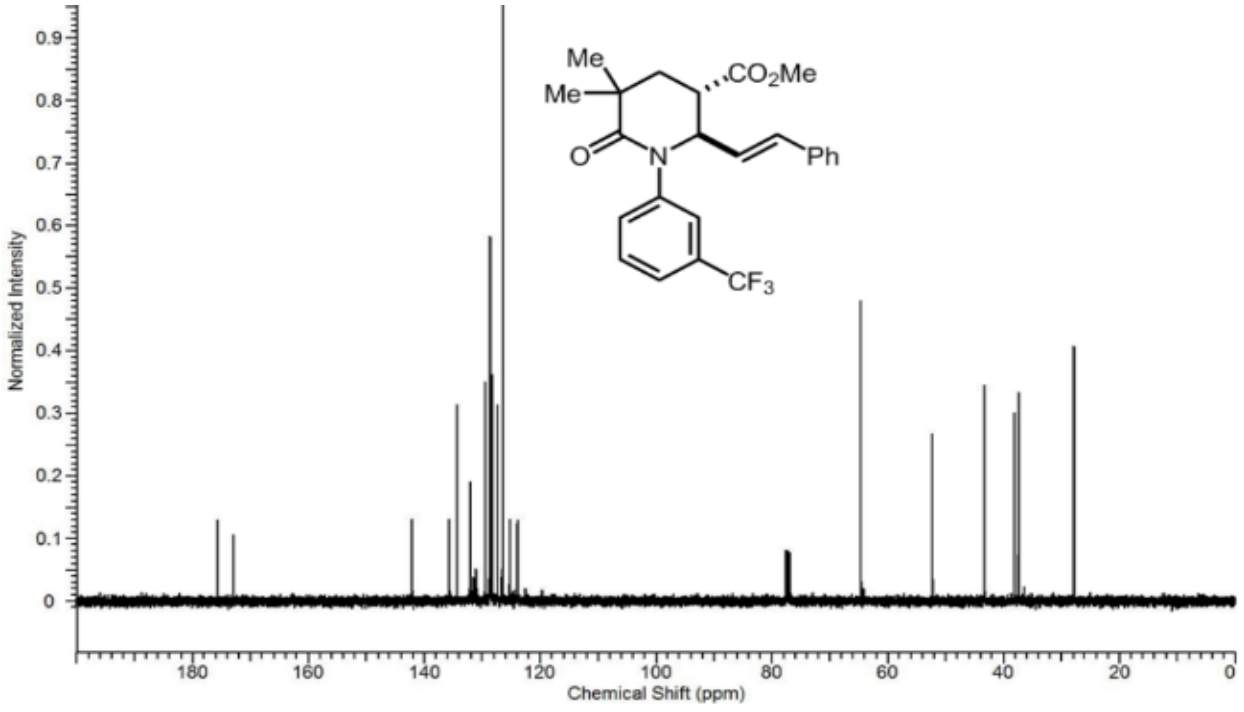
Spectrum 1-**178**: DEPT-135 NMR spectrum of **71H.**



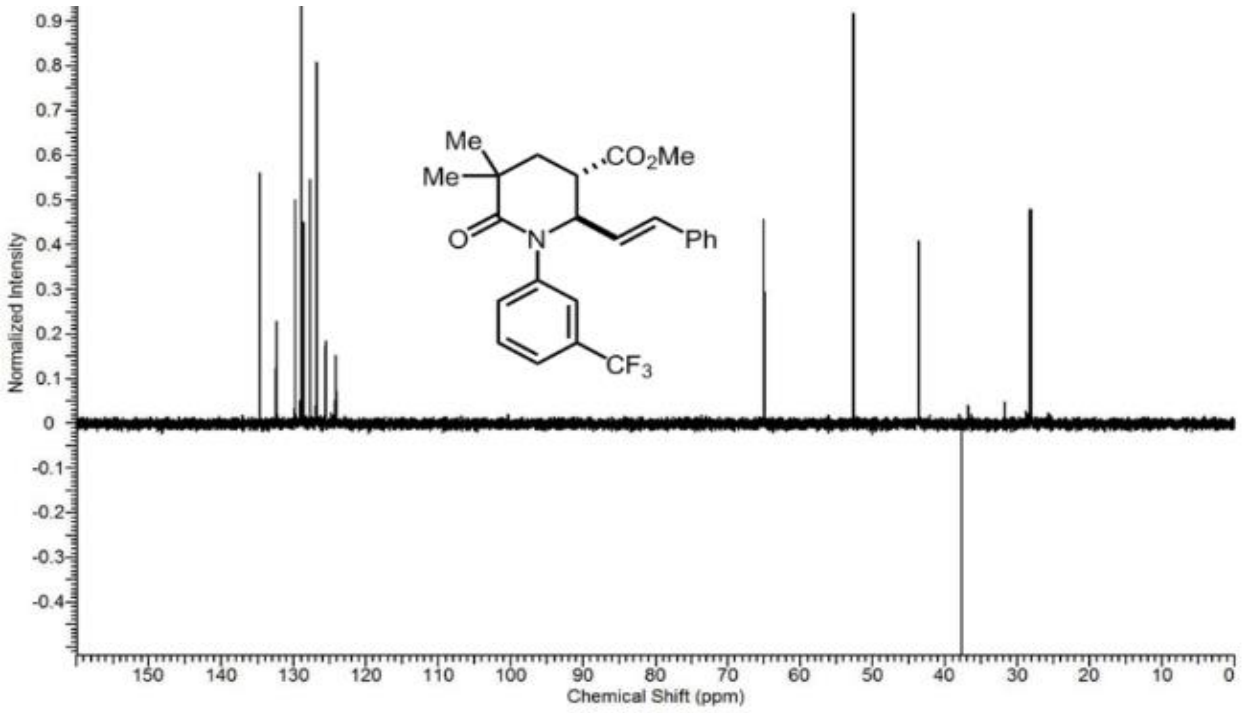
Spectrum 1-**179**: MS spectrum of **7h2.**



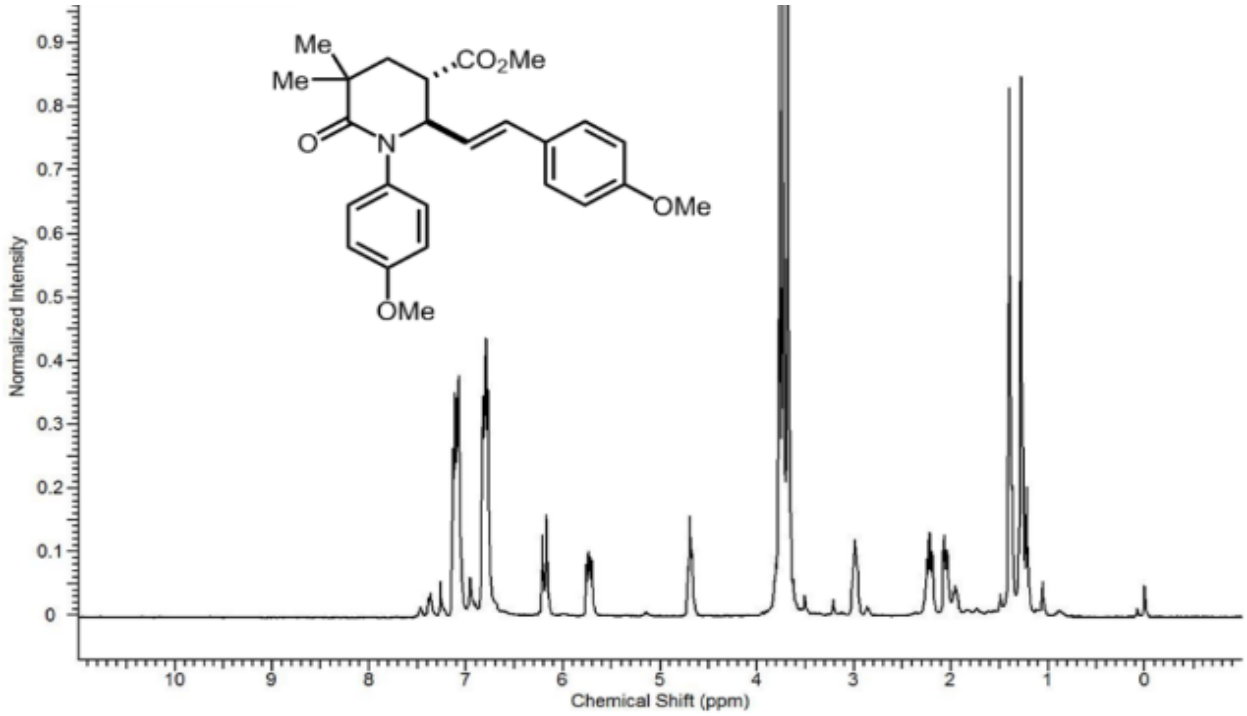
Spectrum 1-**180**: ^{1}H NMR spectrum of **7h2.**



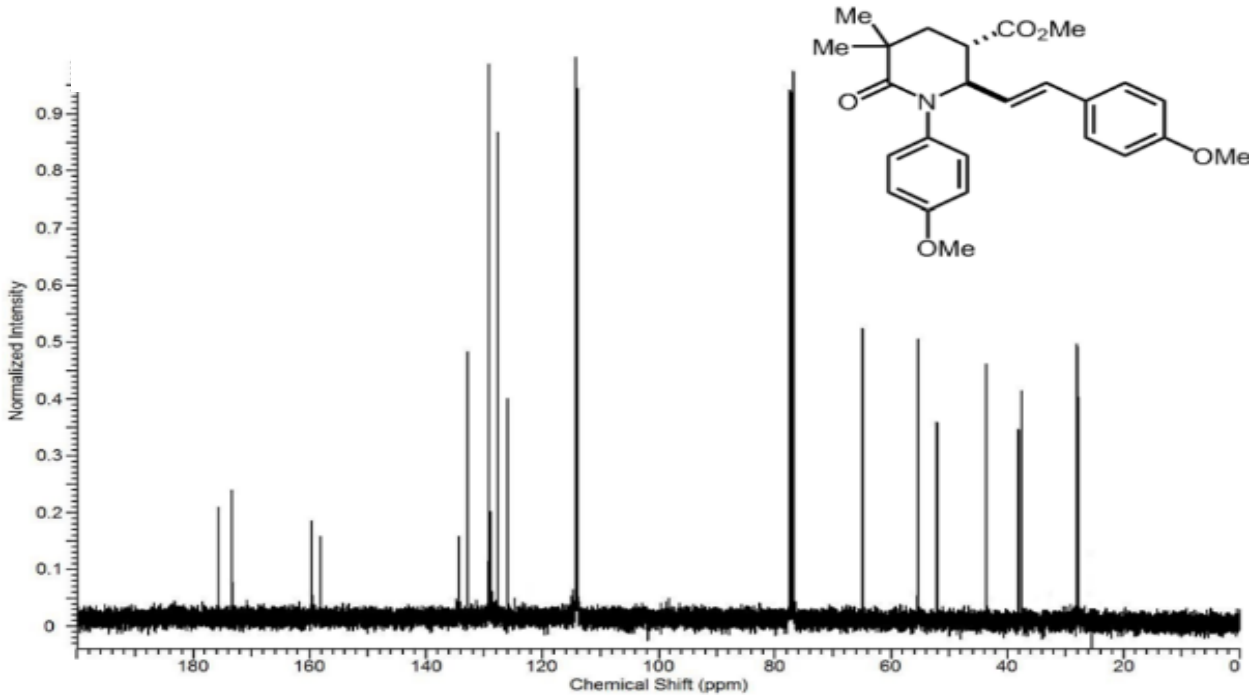
Spectrum 1-**181**: ^{13}C NMR spectrum of **7h2.**



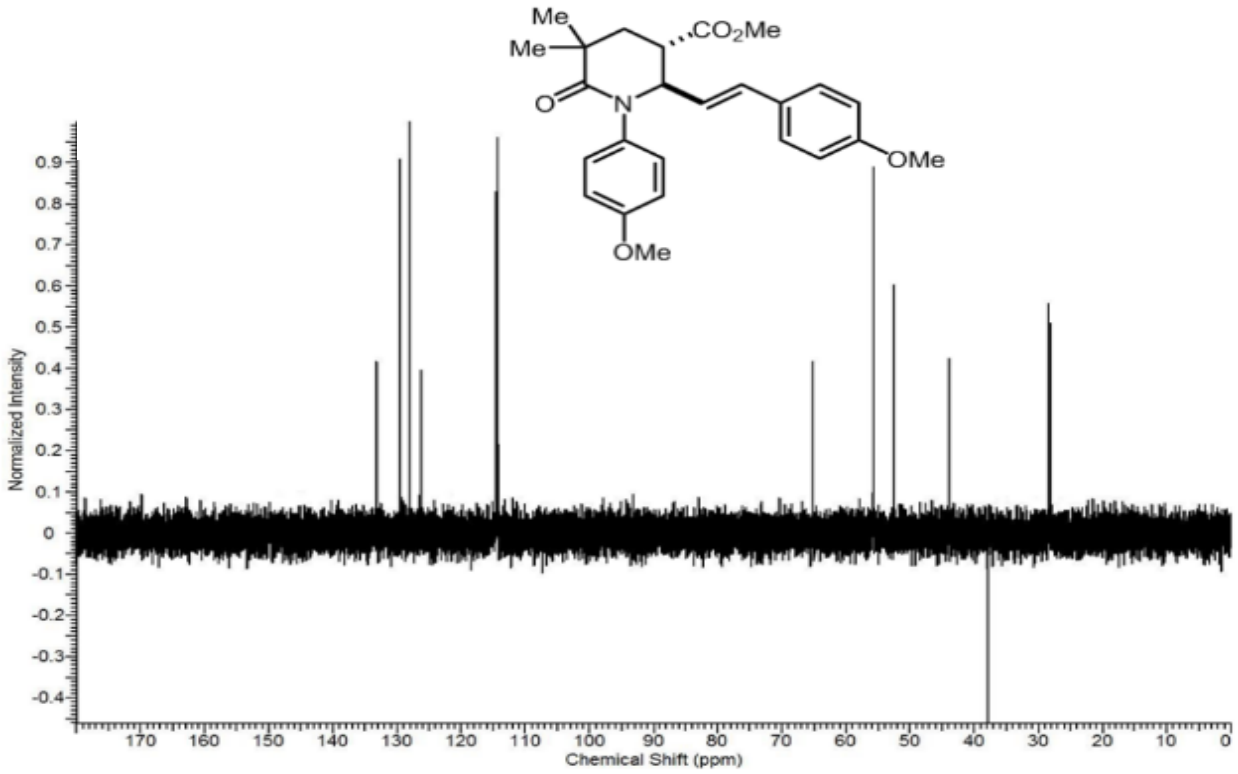
Spectrum 1-**182**: DEPT-135 NMR spectrum of **7h2.**



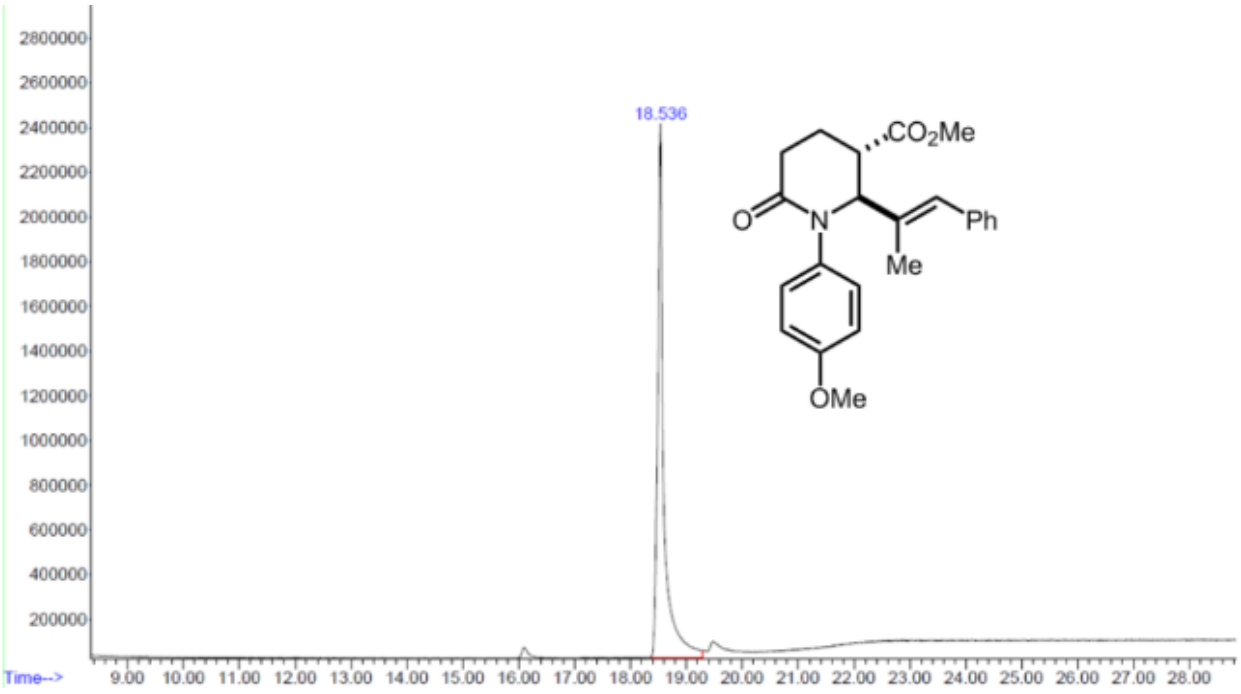
Spectrum 1-**183**: ^{1}H NMR spectrum of **7i2.**



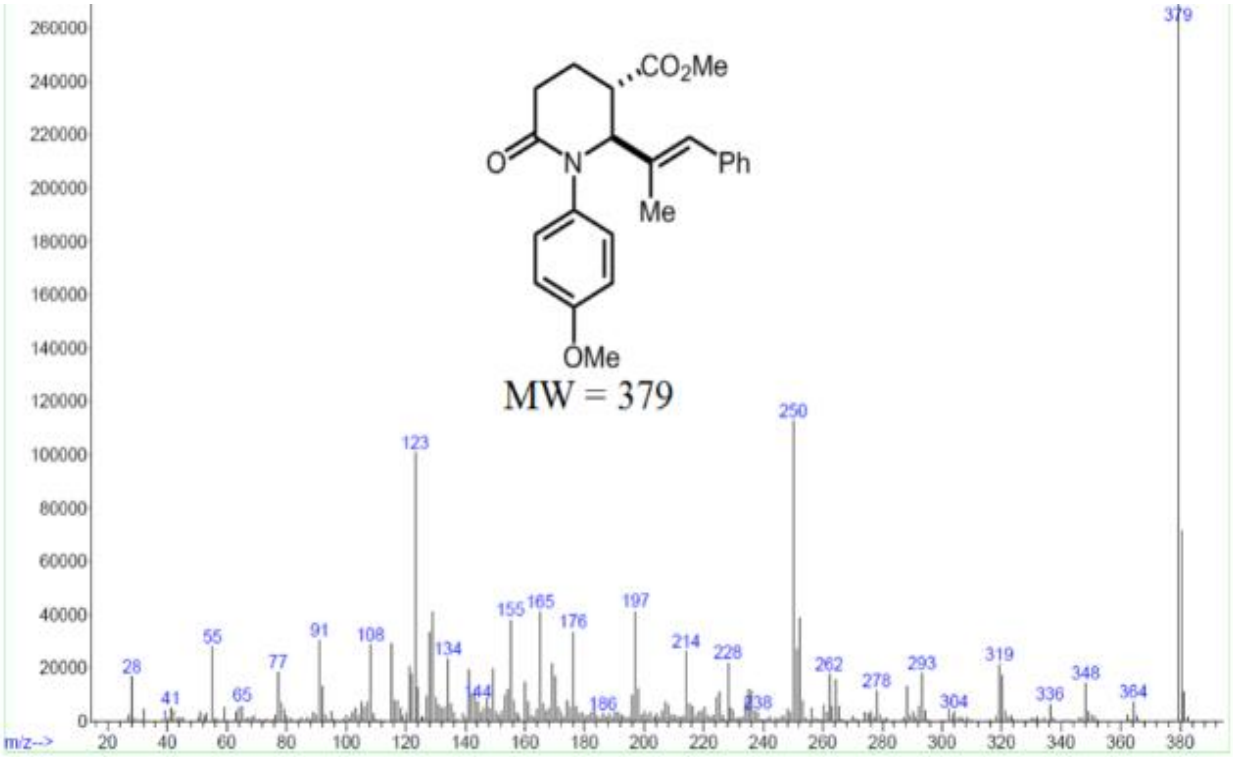
Spectrum 1-**184**: ^{13}C NMR spectrum of **7i2.**



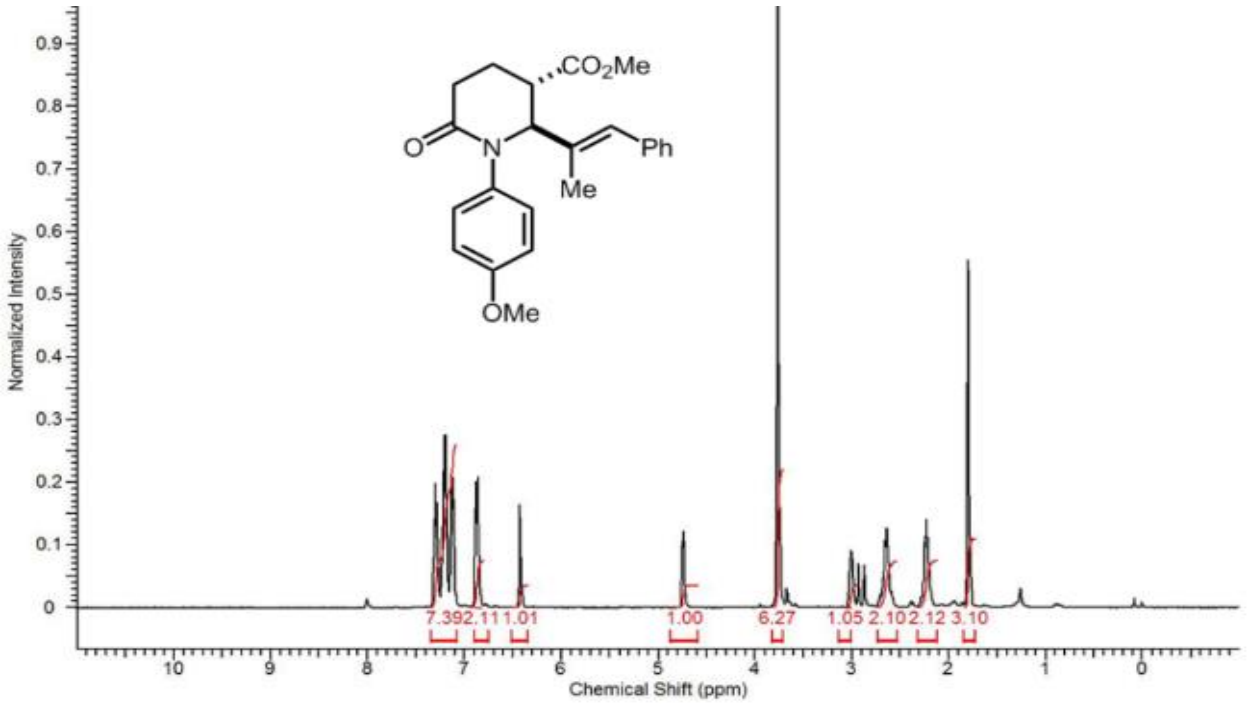
Spectrum 1-**185**: DEPT-135 NMR spectrum of **7i2.**



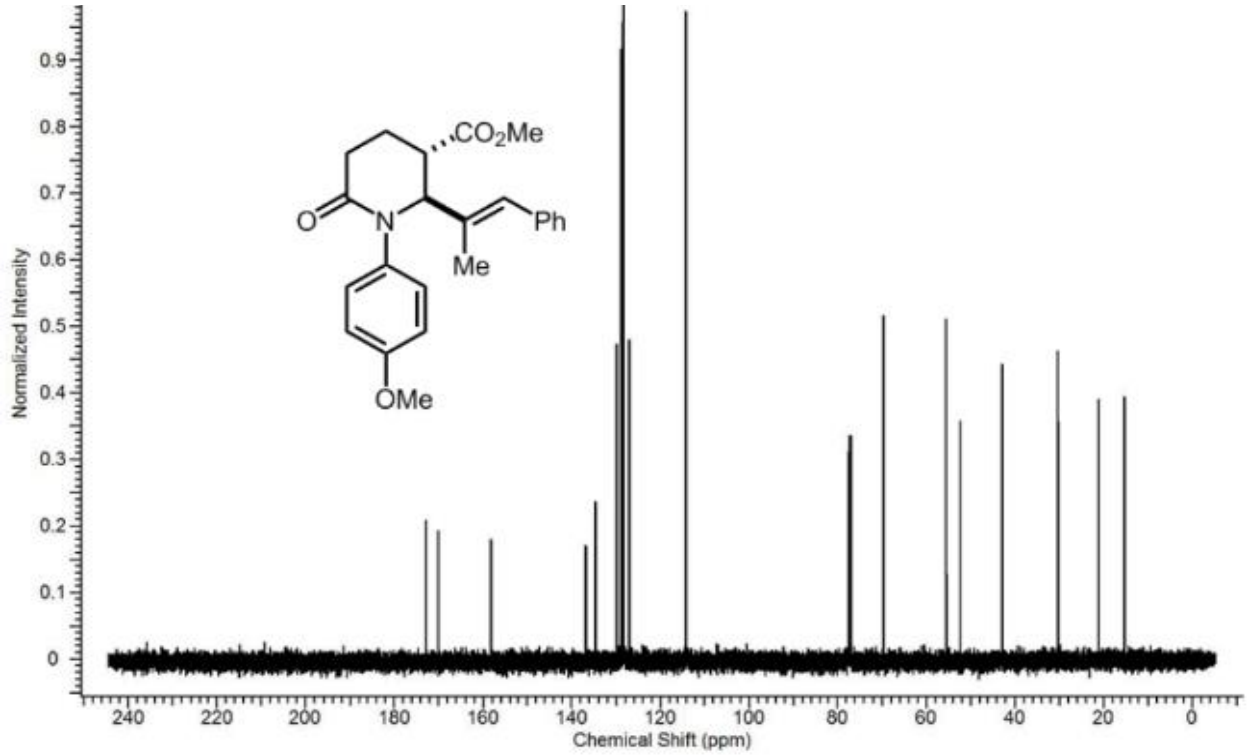
Spectrum 1-**186**: GC spectrum of **7j2.**



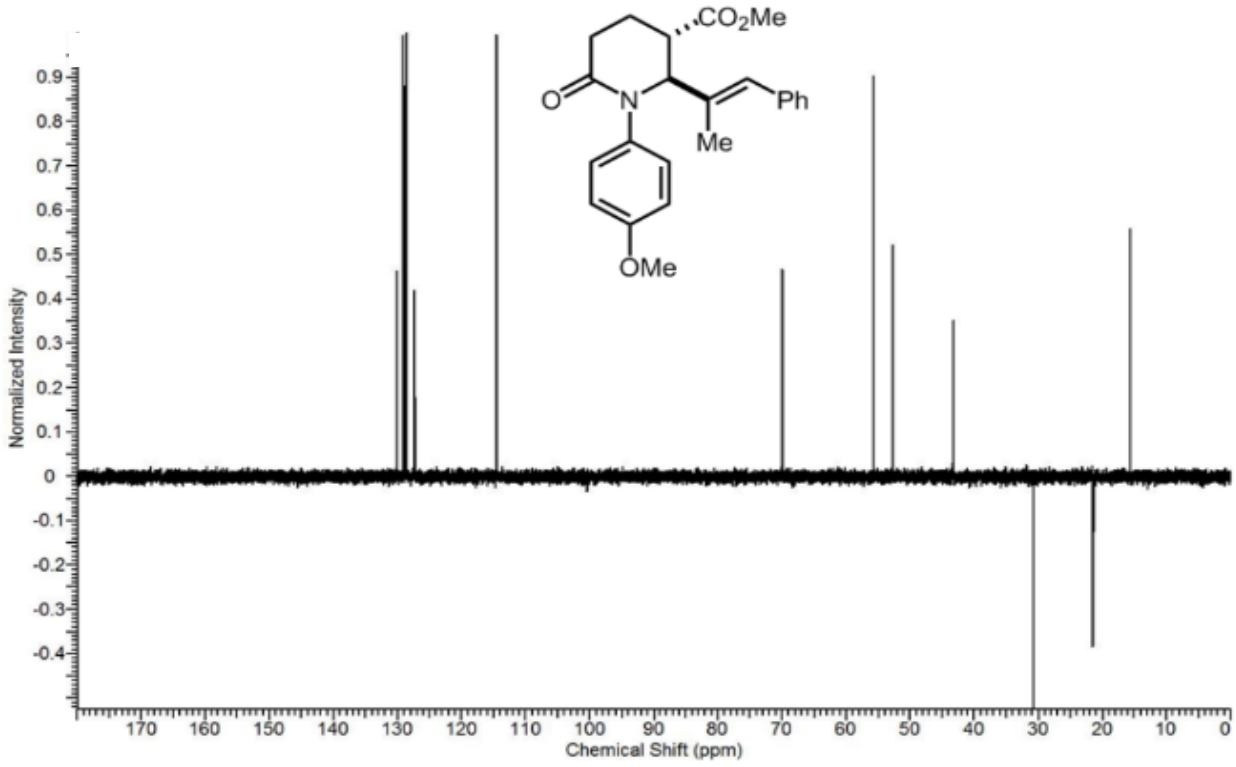
Spectrum 1-**187**: MS spectrum of **7j2**.



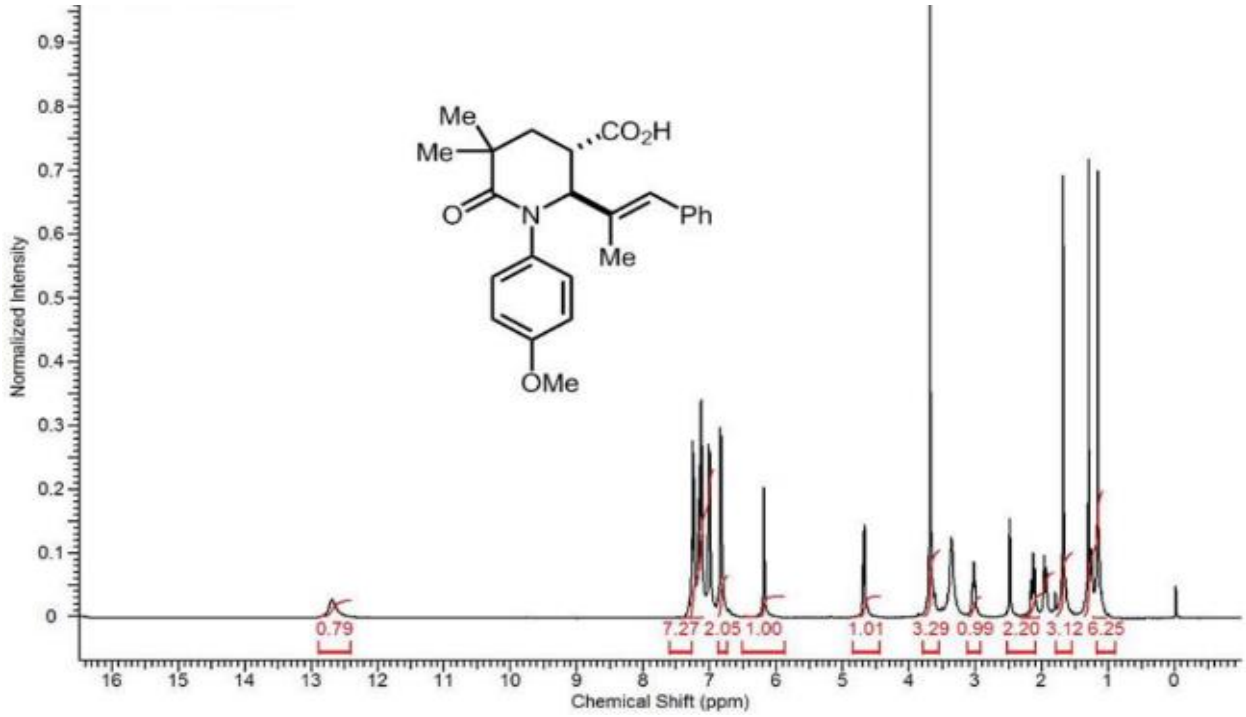
Spectrum 1-**188**: ^{1}H NMR spectrum of **7h2.**



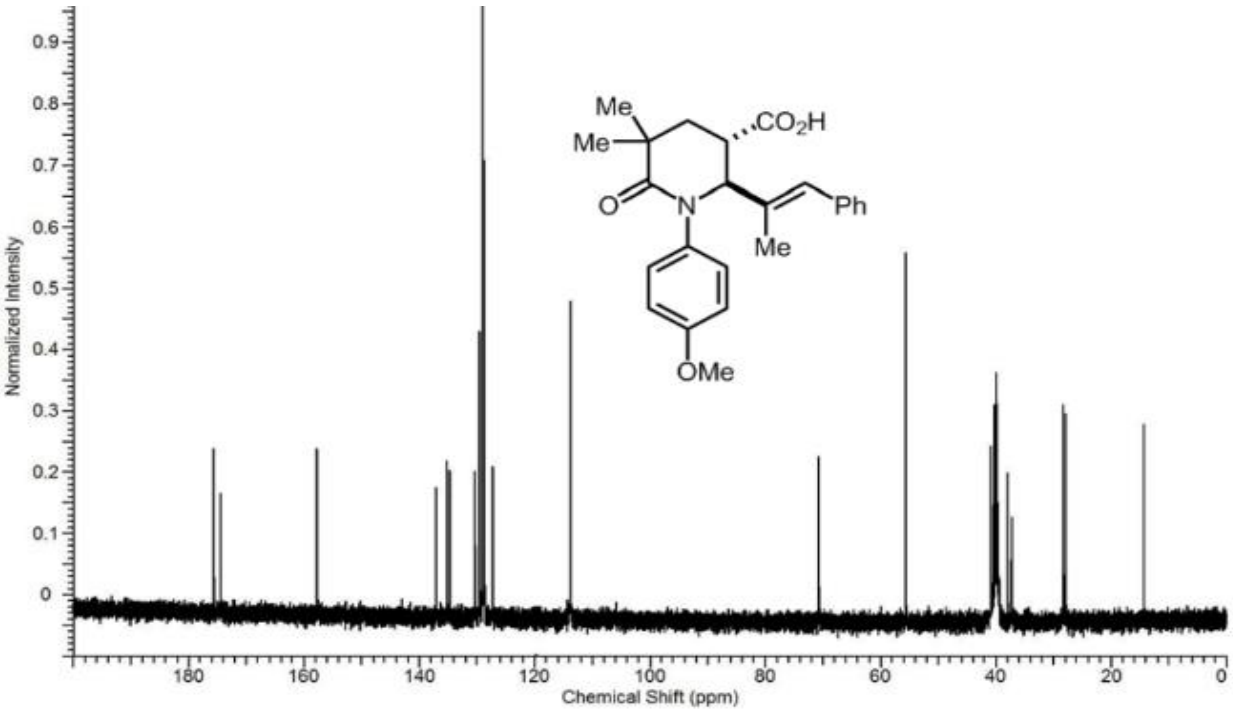
Spectrum 1-**189**: ^{13}C NMR spectrum of **7j2.**



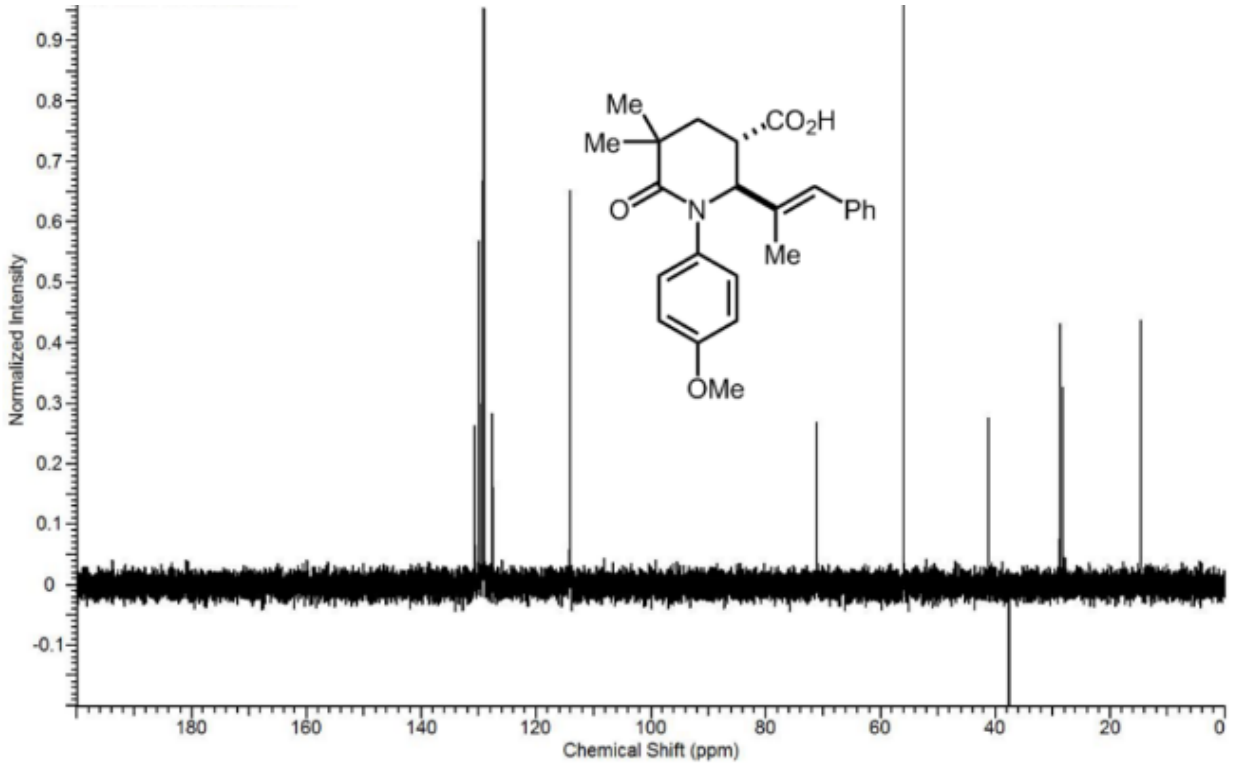
Spectrum 1-**190**: DEPT-135 NMR spectrum of **7j2.**



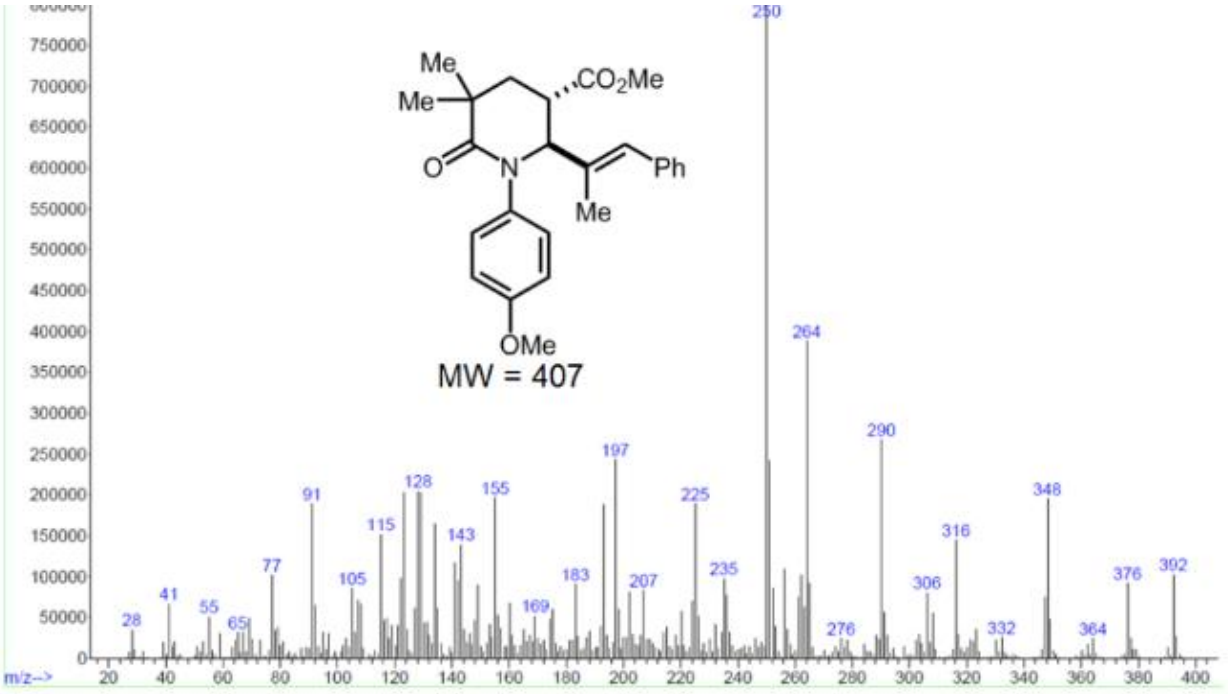
Spectrum 1-**191**: ^{1}H NMR spectrum of **7k1.**



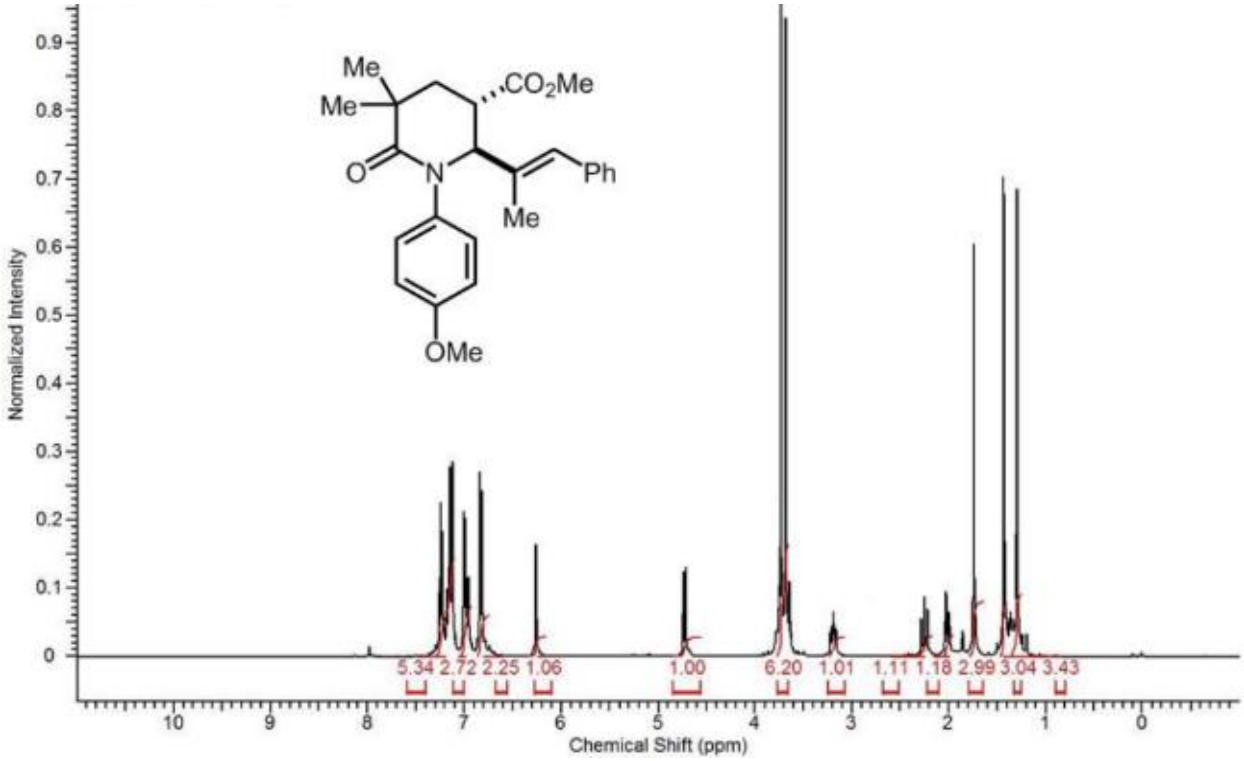
Spectrum 1-**192**: ^{13}C NMR spectrum of **7k1.**



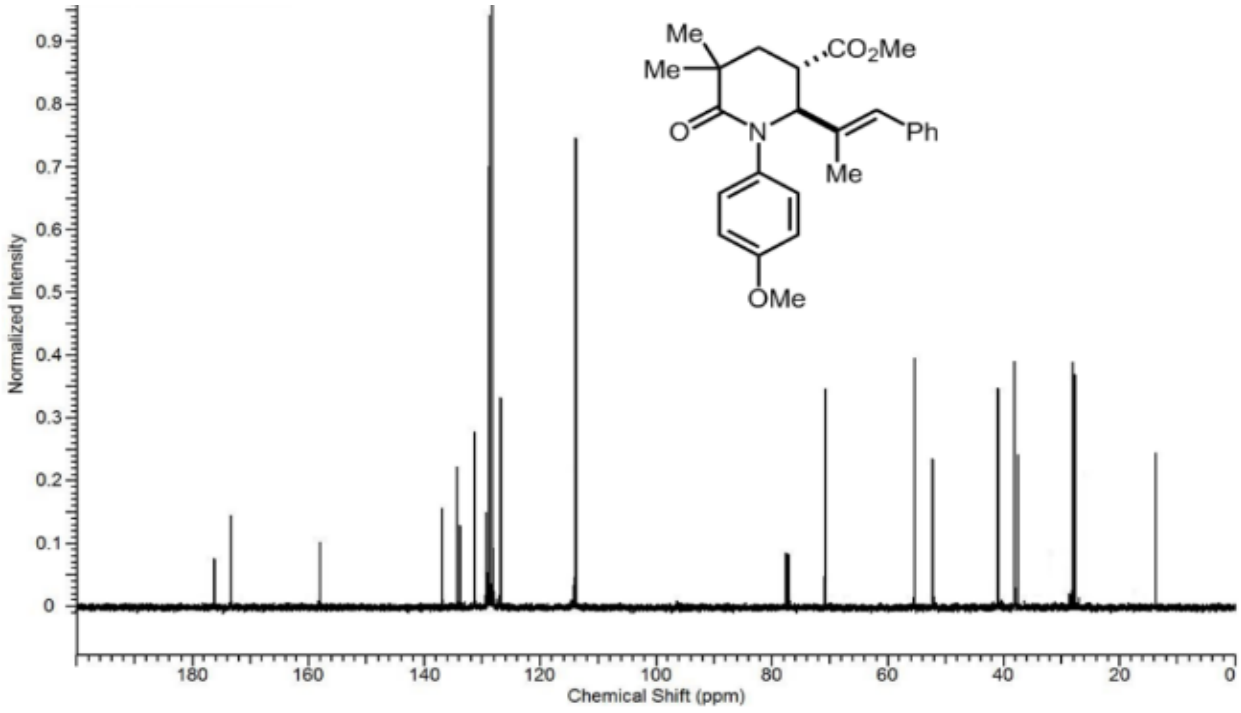
Spectrum 1-**193**: DEPT-135 NMR spectrum of **7k1.**



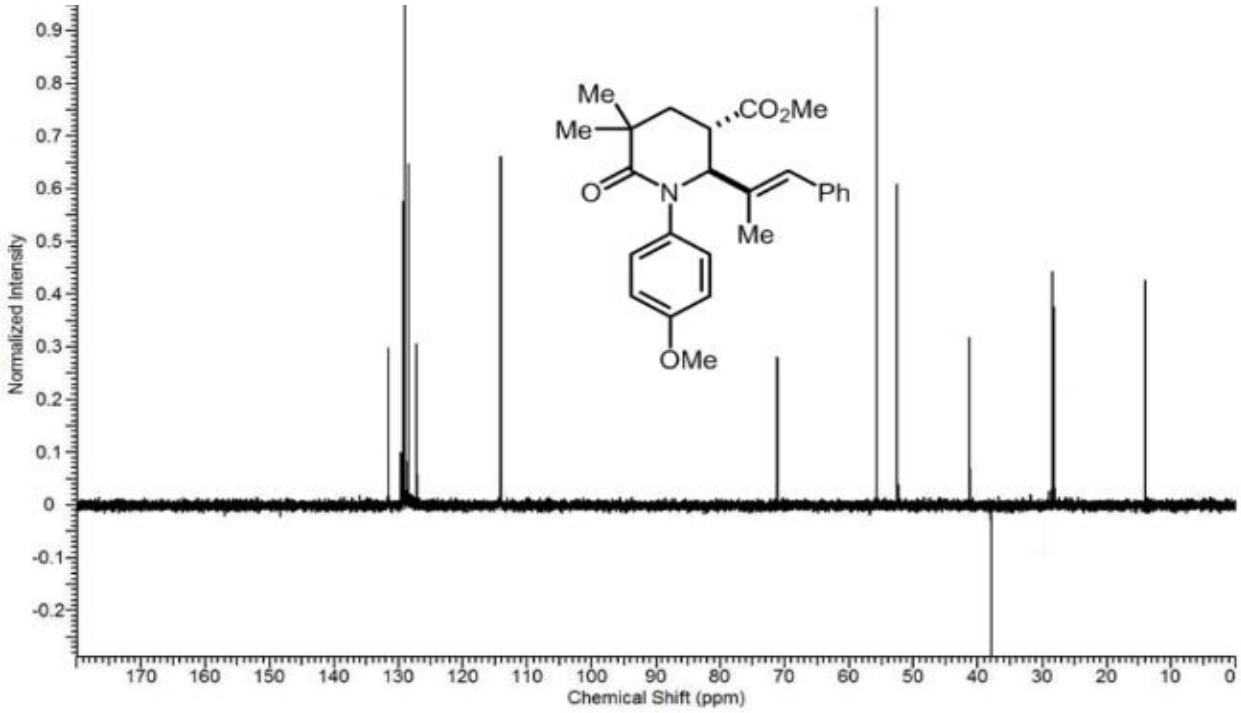
Spectrum 1-**194**: MS spectrum of **7k2.**



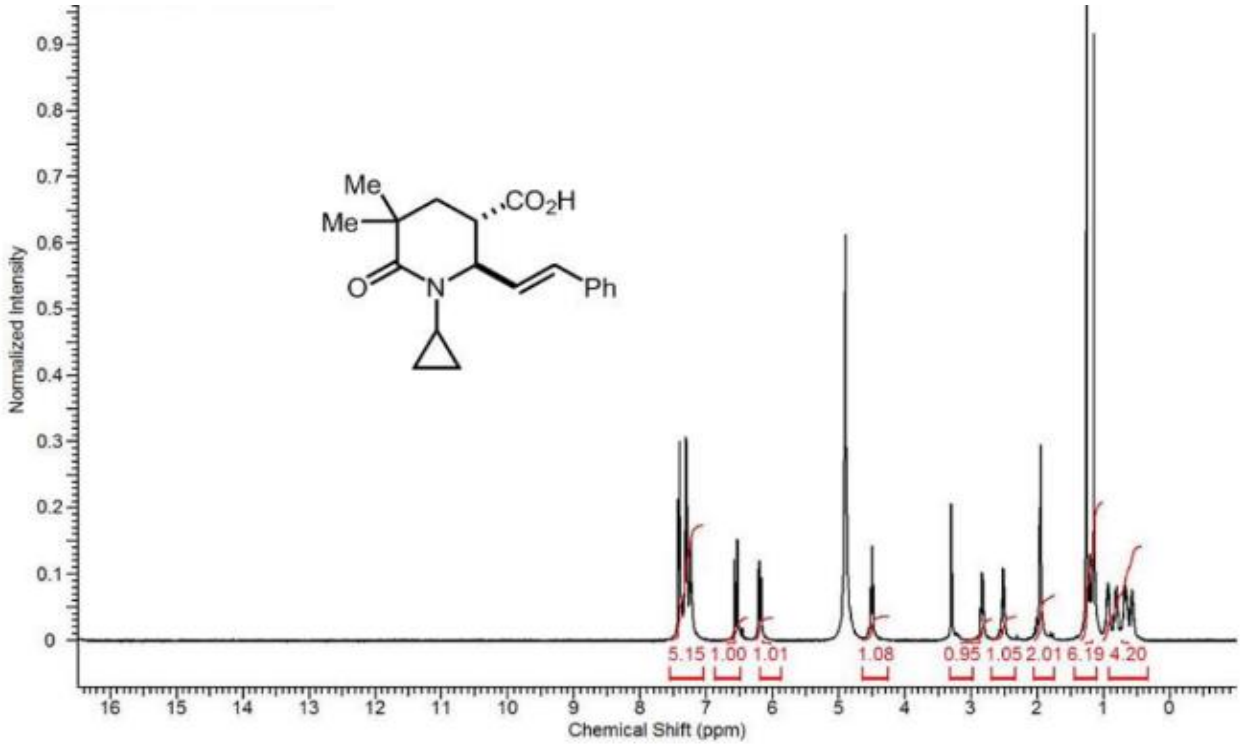
Spectrum 1-**195**: ^{1}H NMR spectrum of **7k2.**



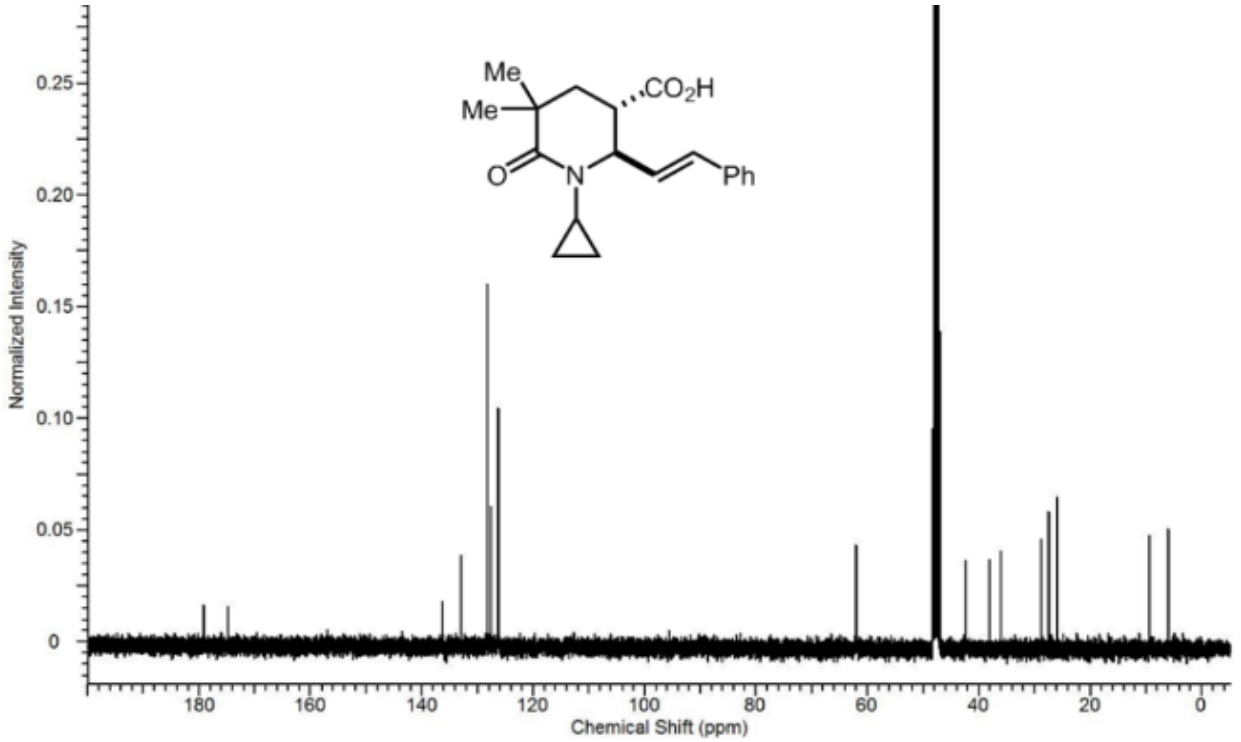
Spectrum 1-**196**: ^{13}C NMR spectrum of **7k2.**



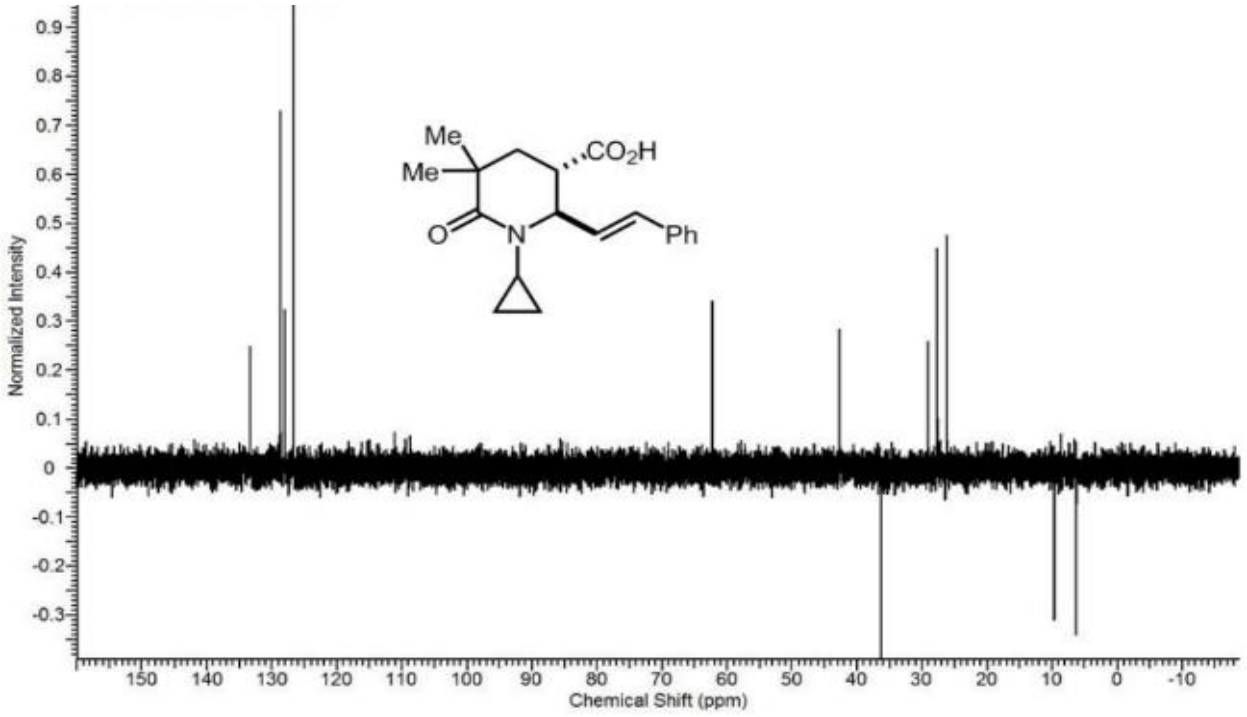
Spectrum 1-**197**: DEPT-135 NMR spectrum of **7k2.**



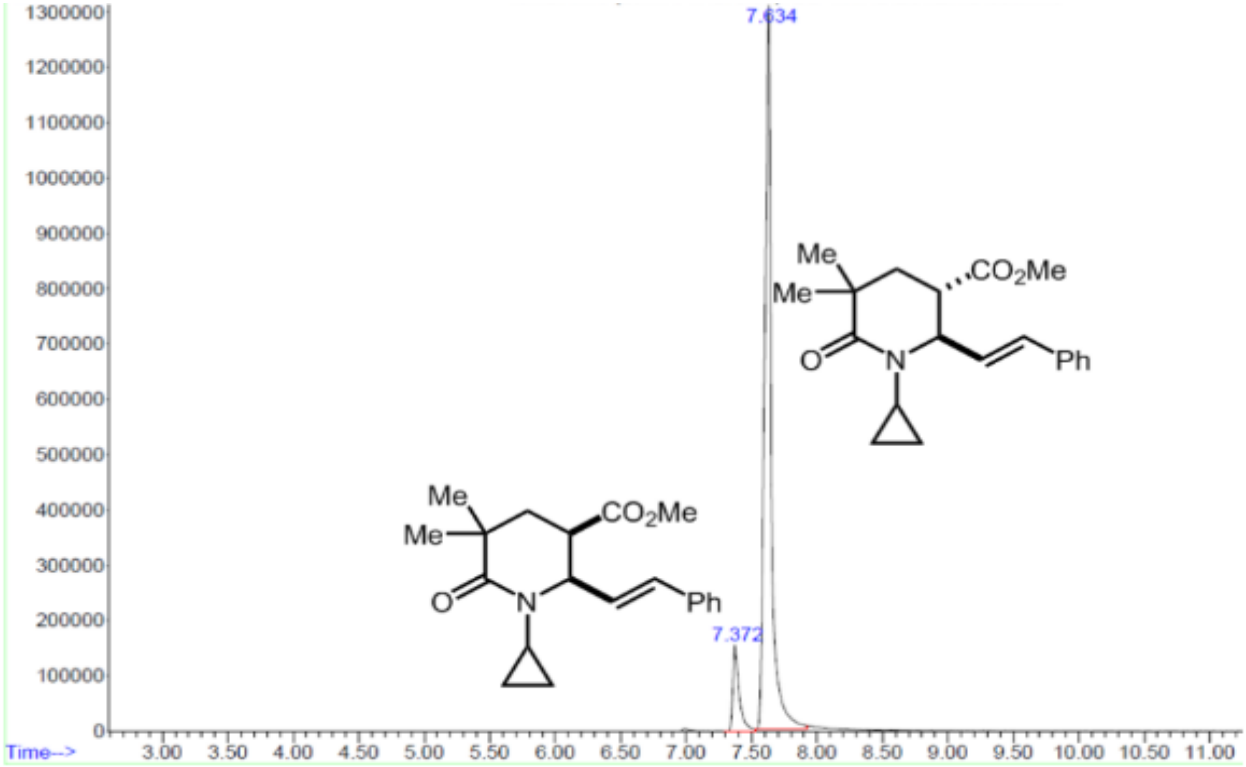
Spectrum 1-**198**: ^{1}H NMR spectrum of **7l1.**



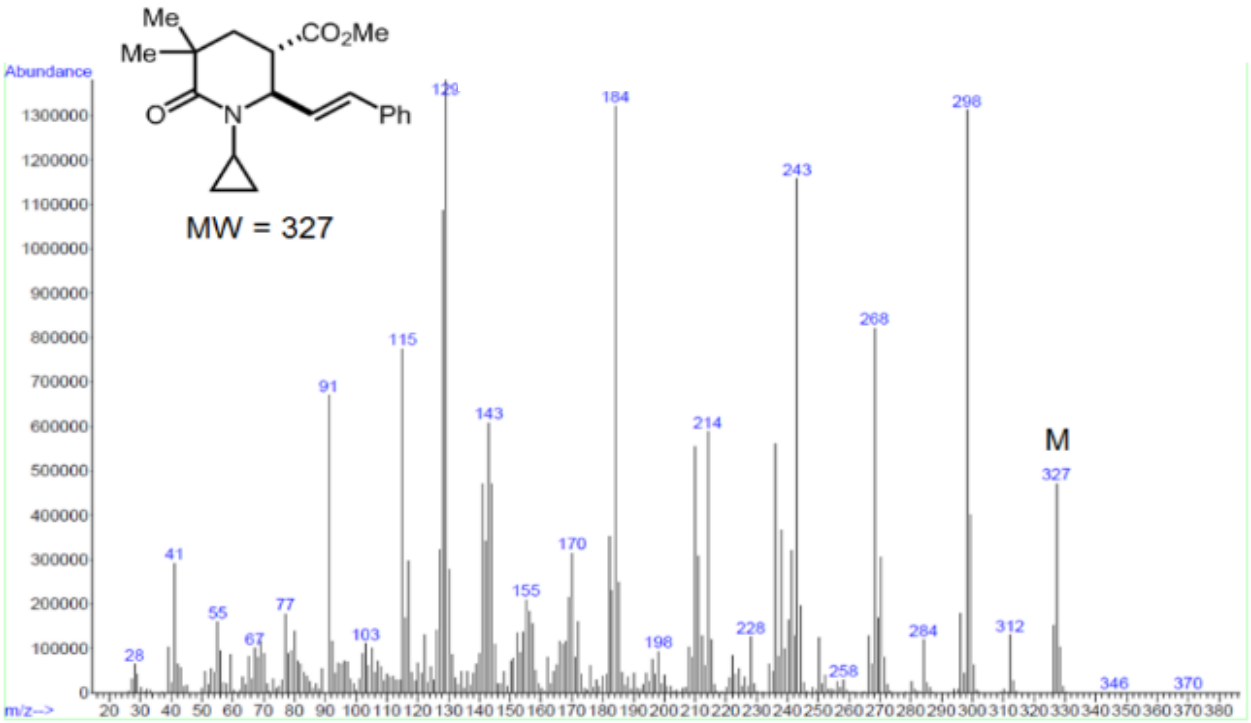
Spectrum 1-**199**: ^{13}C NMR spectrum of **7l1.**



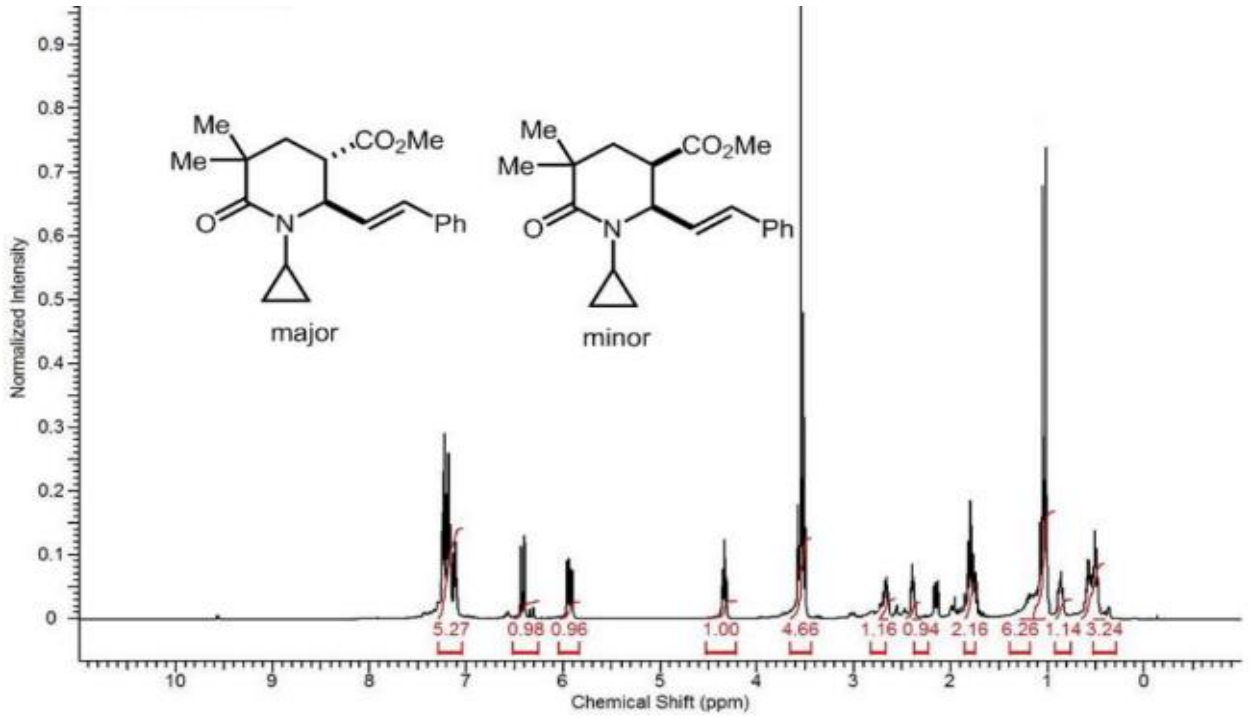
Spectrum 1-**200**: DEPT-135 NMR spectrum of **7l1.**



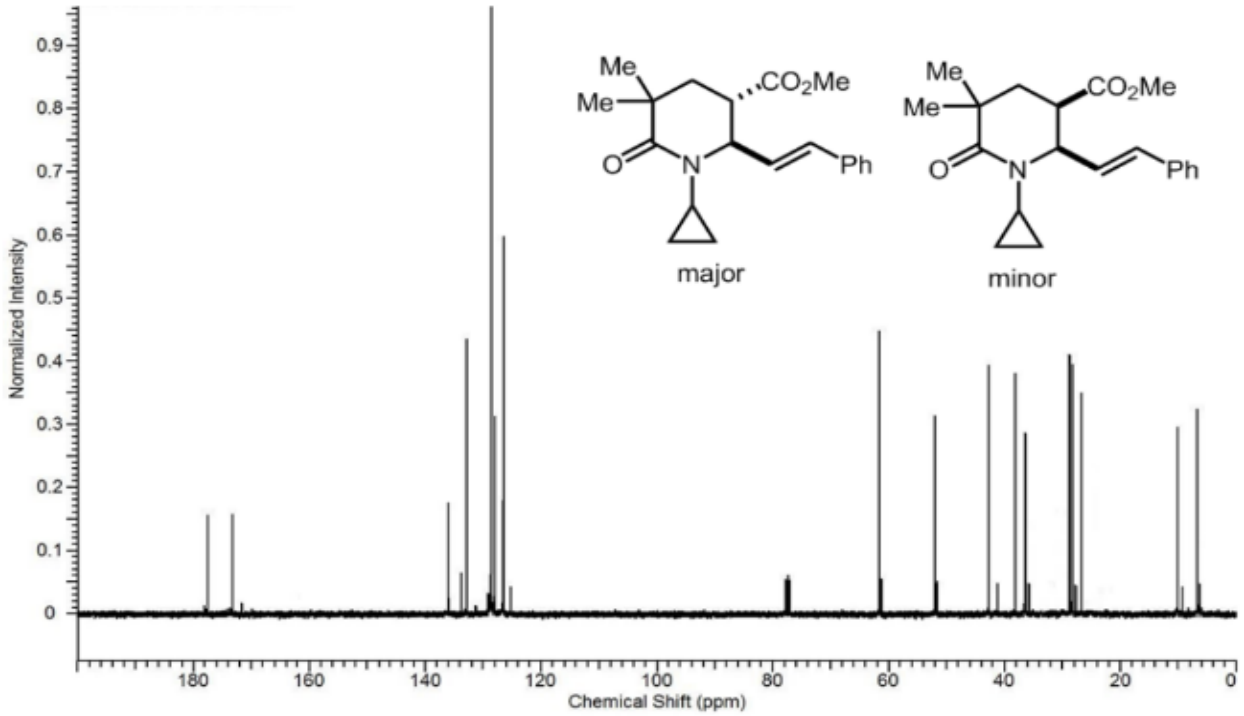
Spectrum 1-**201**: GC spectrum of **7l2.**



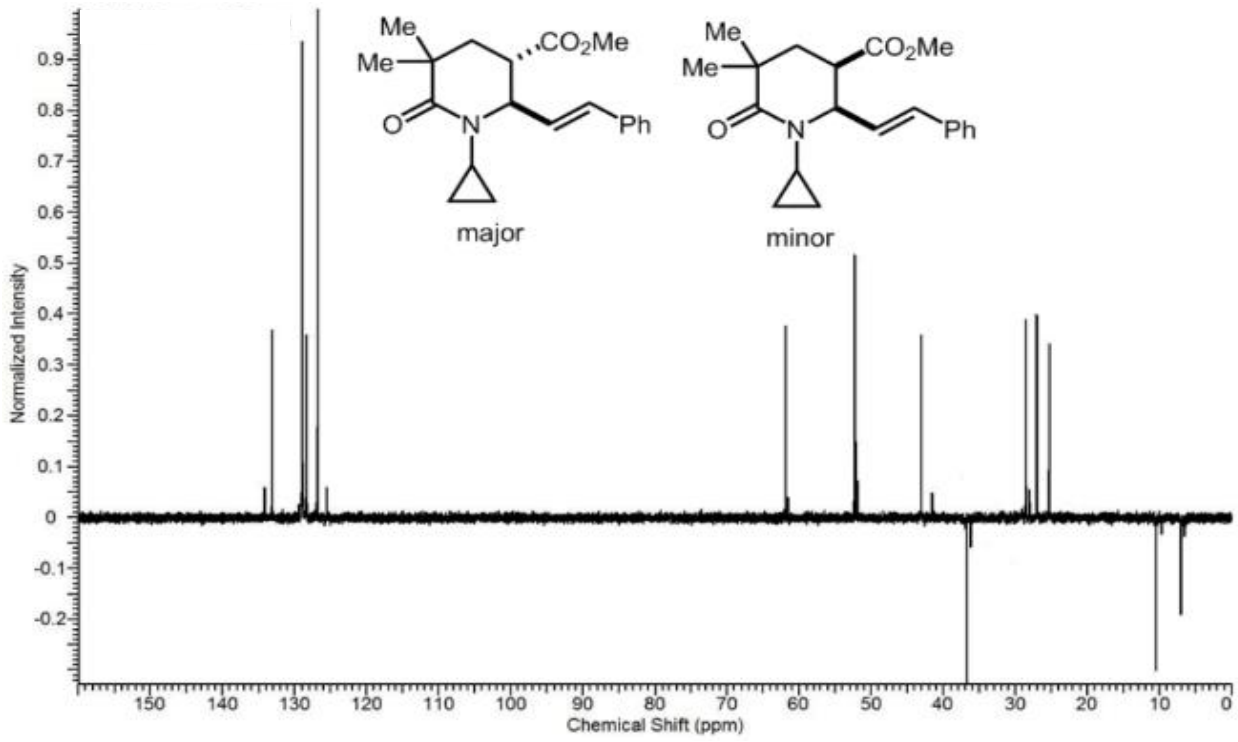
Spectrum 1-**202**: MS spectrum of **7l2.**



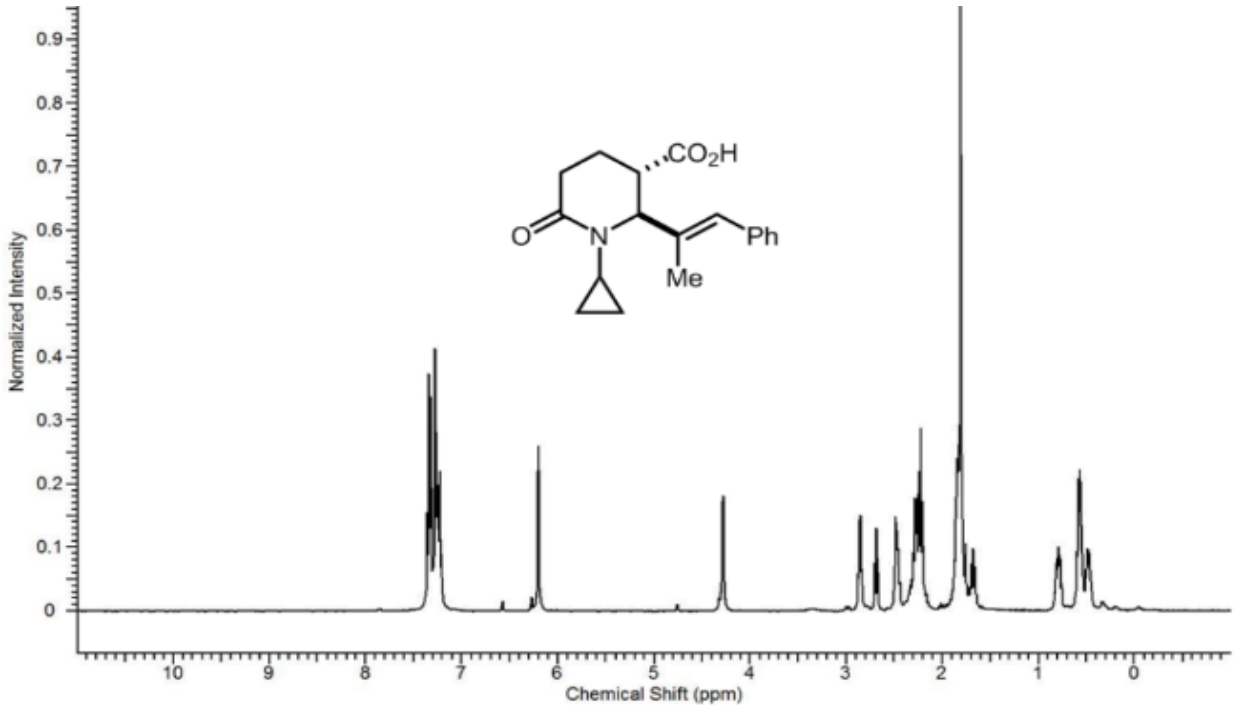
Spectrum 1-**203**: ^{1}H NMR spectrum of **7l2.**



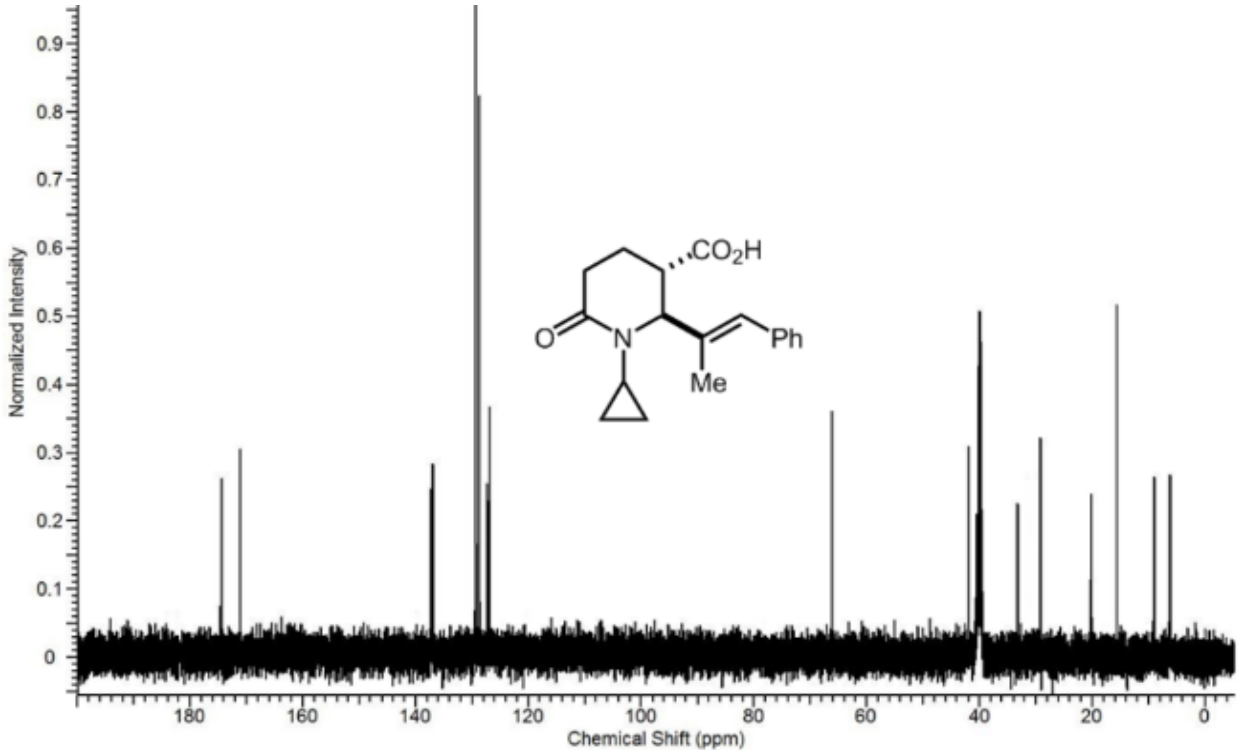
Spectrum 1-**204**: ^{13}C NMR spectrum of **7l2.**



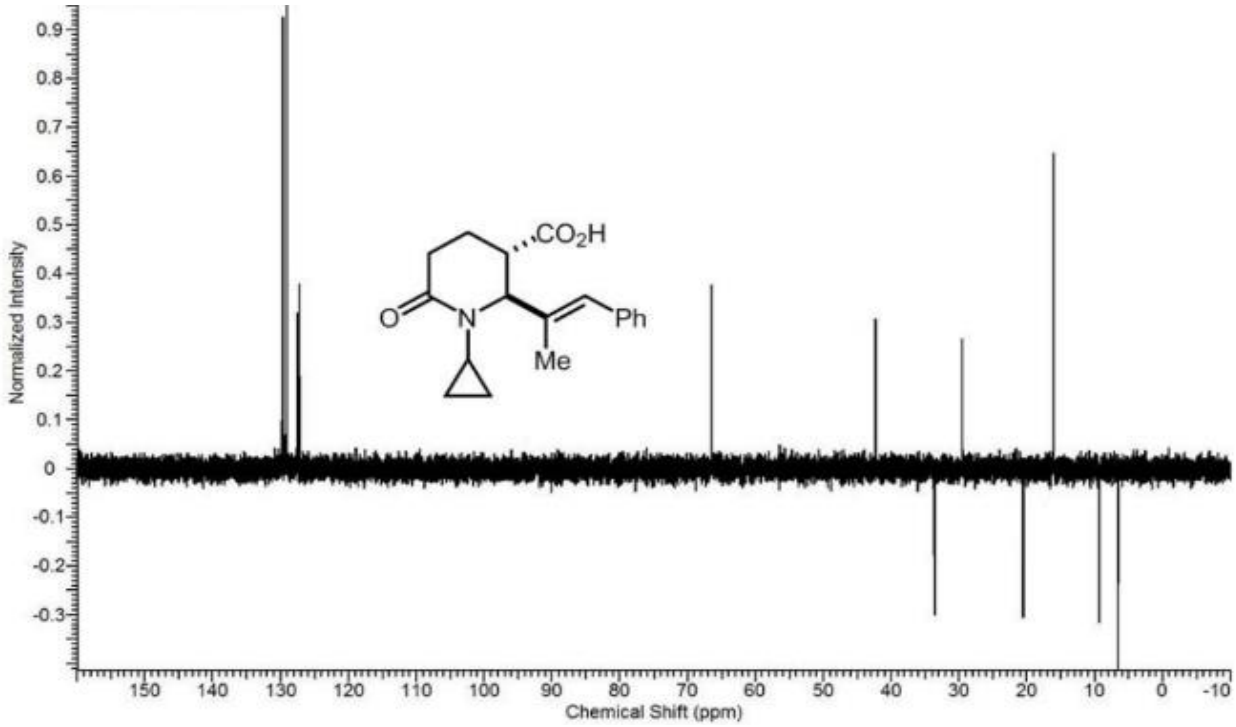
Spectrum 1-**205**: DEPT-135 NMR spectrum of **7l2.**



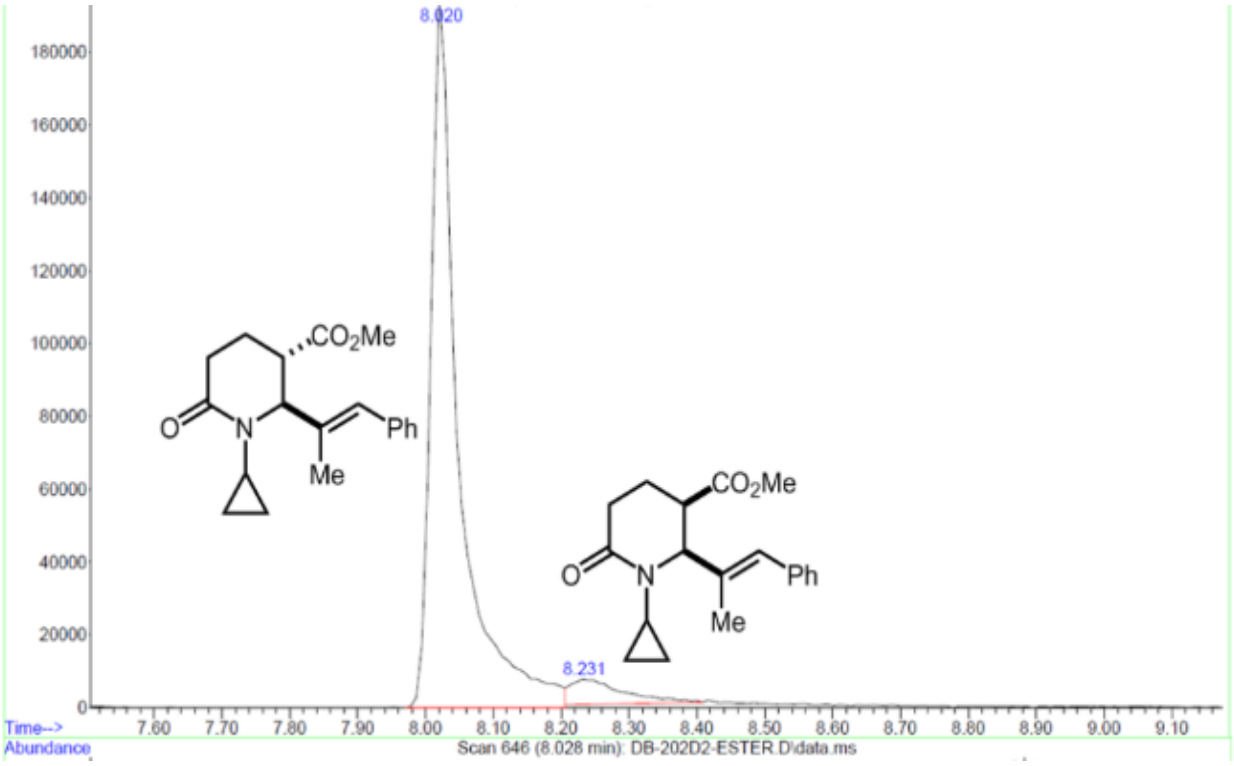
Spectrum 1-**206**: ^{1}H NMR spectrum of **7m1.**



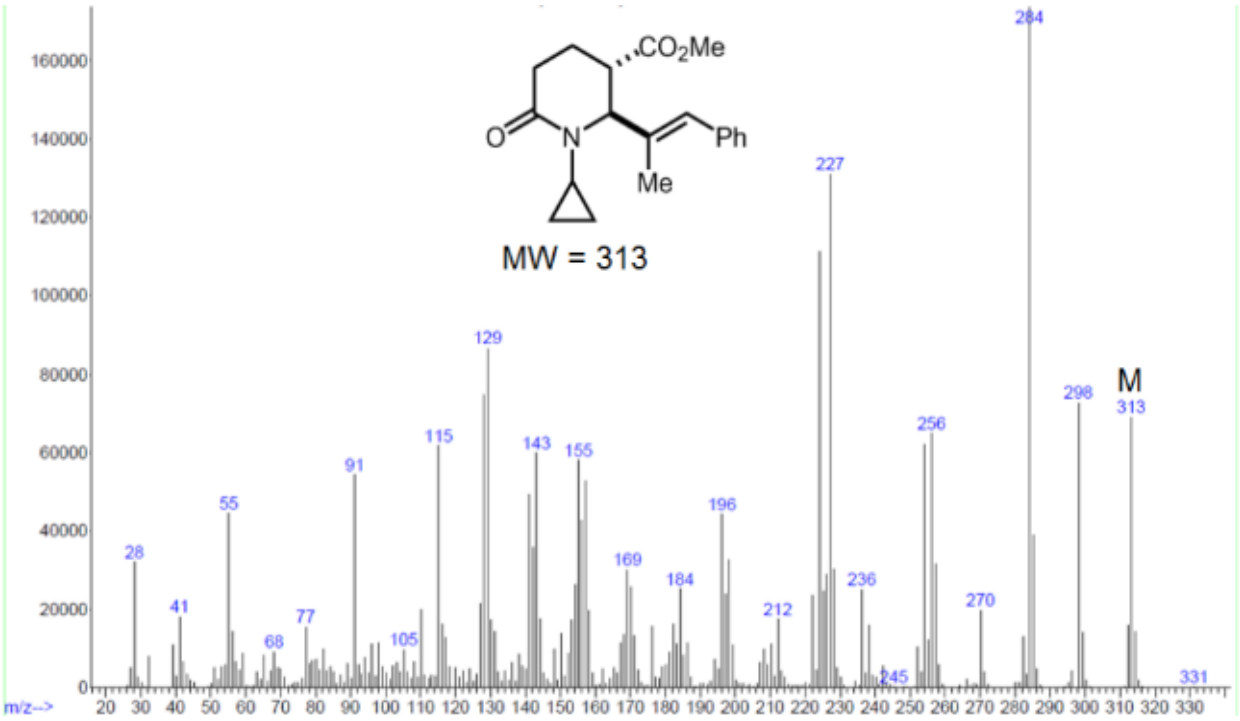
Spectrum 1-**207**: ^{13}C NMR spectrum of **7m1.**



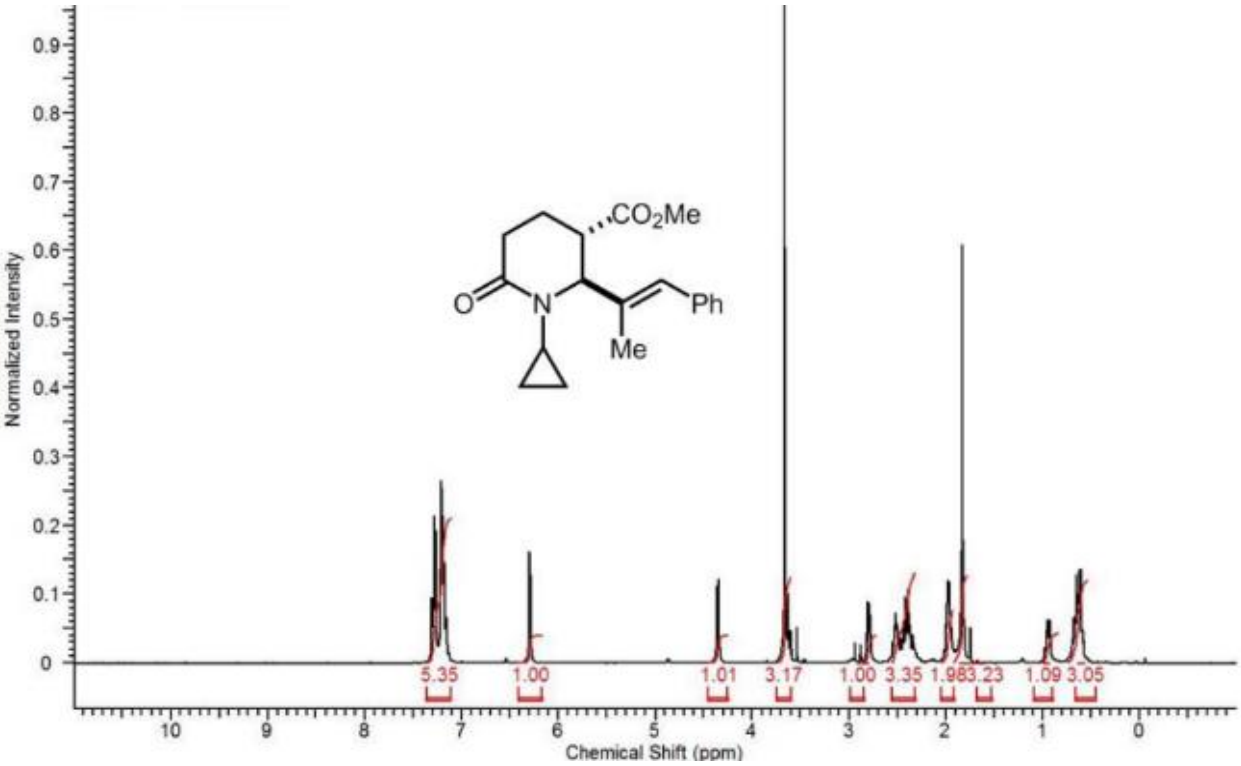
Spectrum 1-**208**: DEPT-135 NMR spectrum of **7m1.**



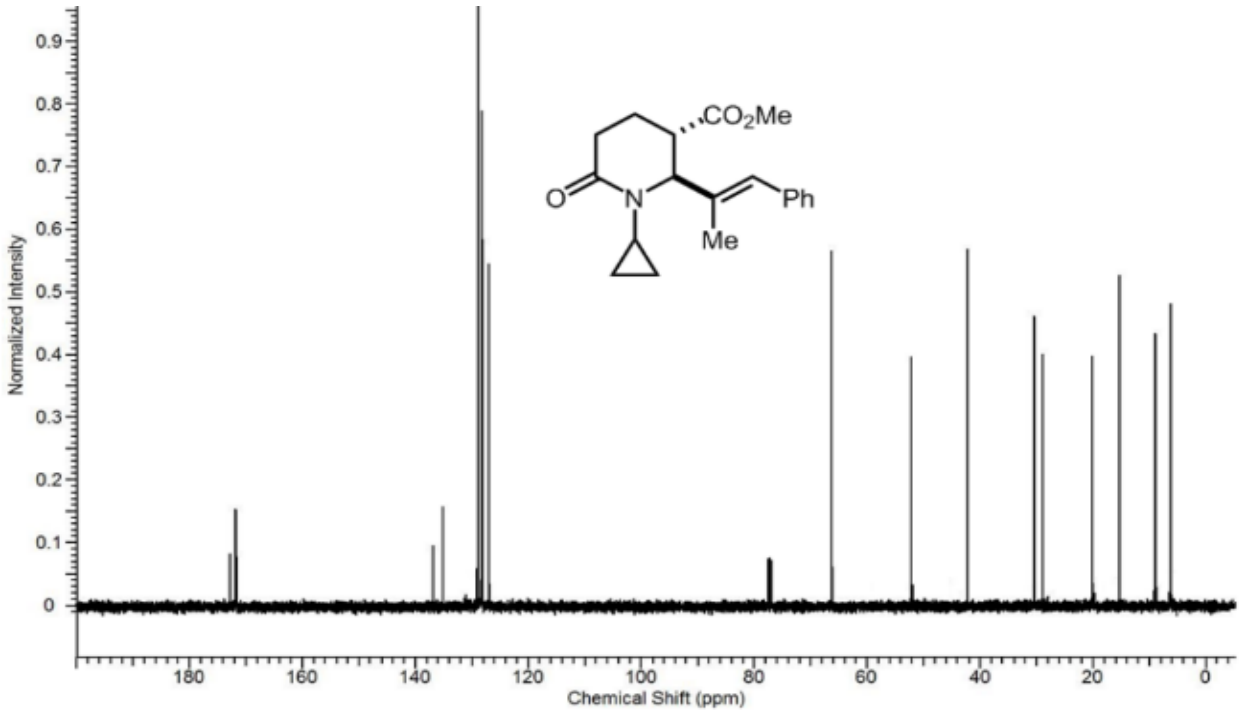
Spectrum 1-**209**: GC spectrum of **7m2.**



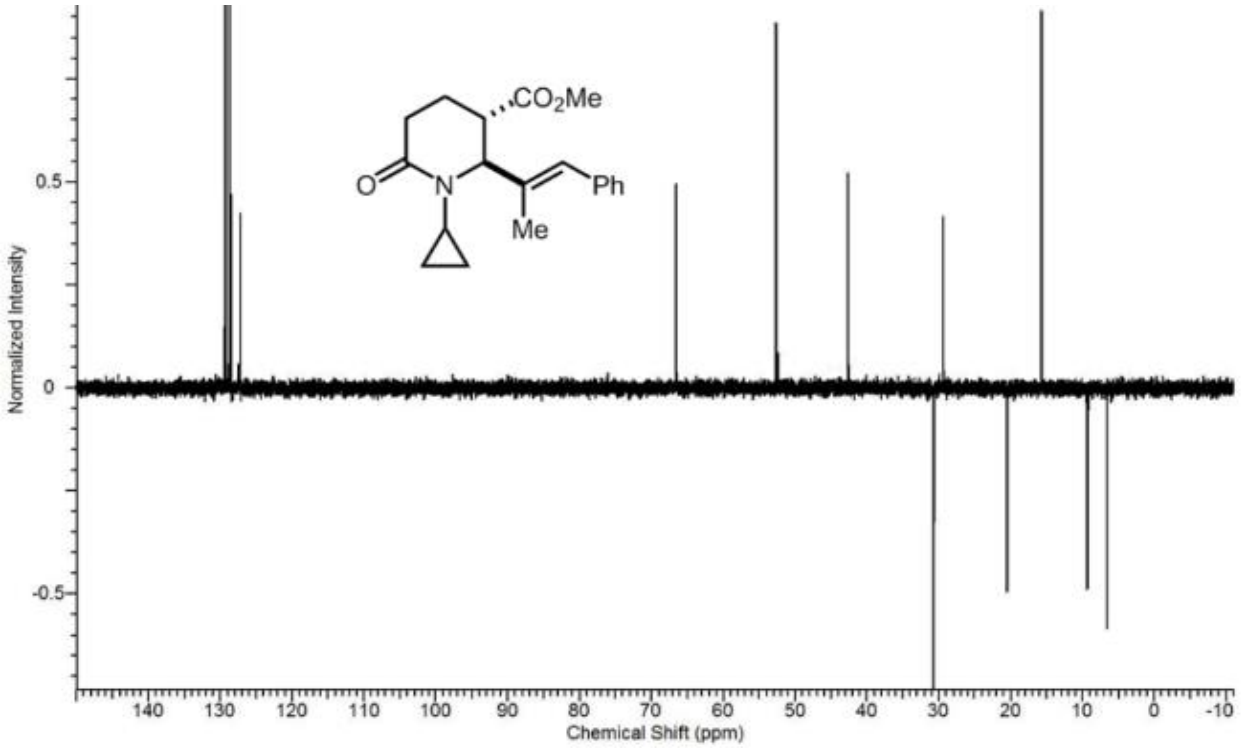
Spectrum 1-**210**: MS spectrum of **7m2.**



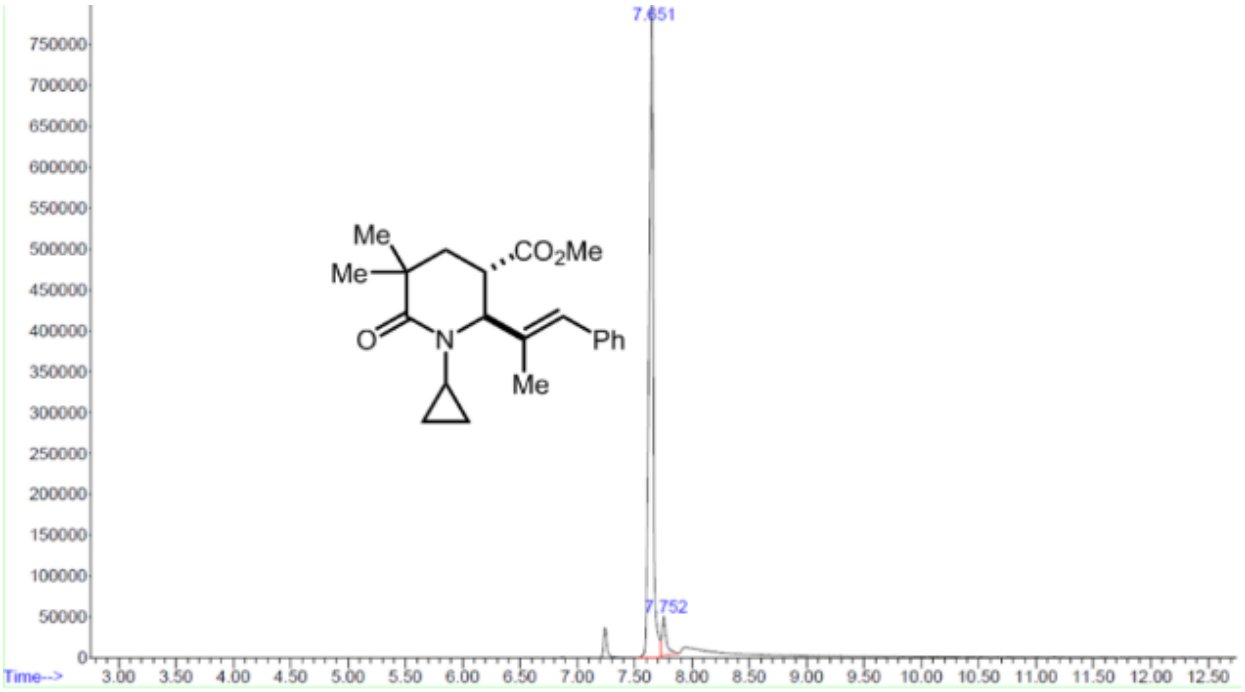
Spectrum 1-**211**: ^{1}H NMR spectrum of **7m2.**



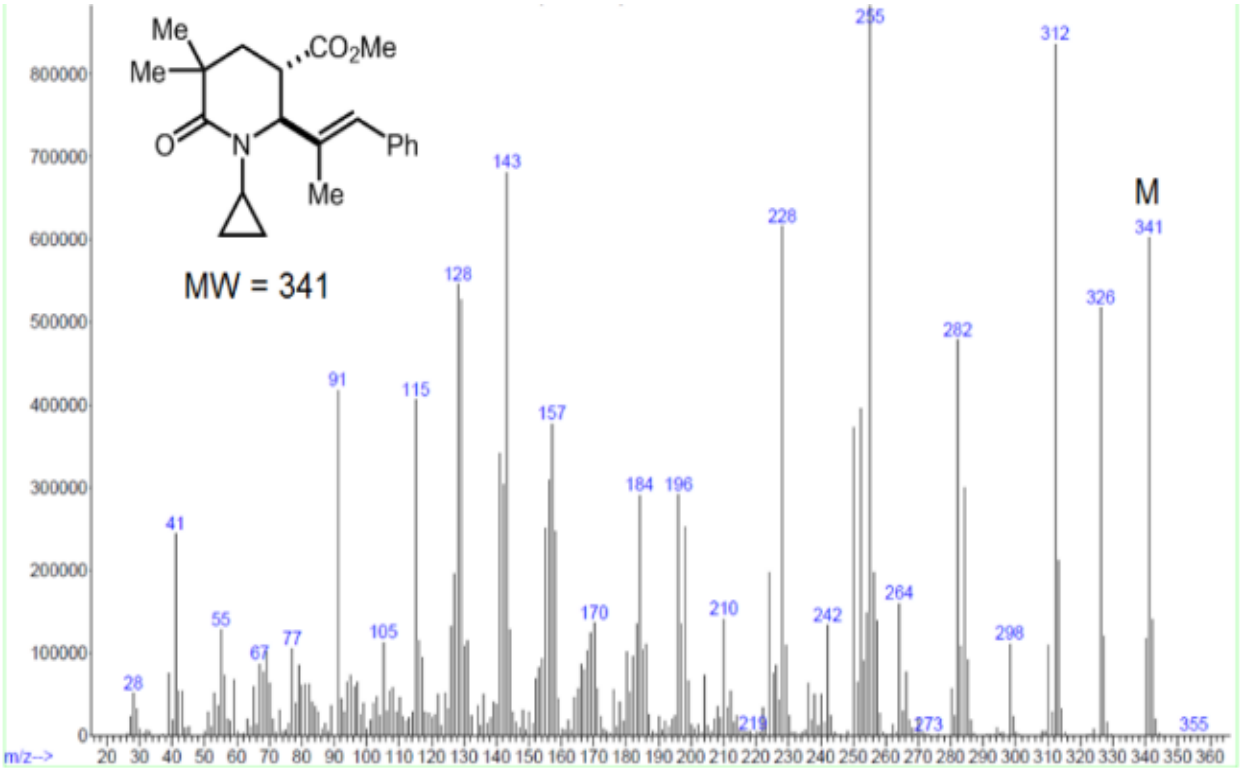
Spectrum 1-**212**: ^{13}C NMR spectrum of **7m2.**



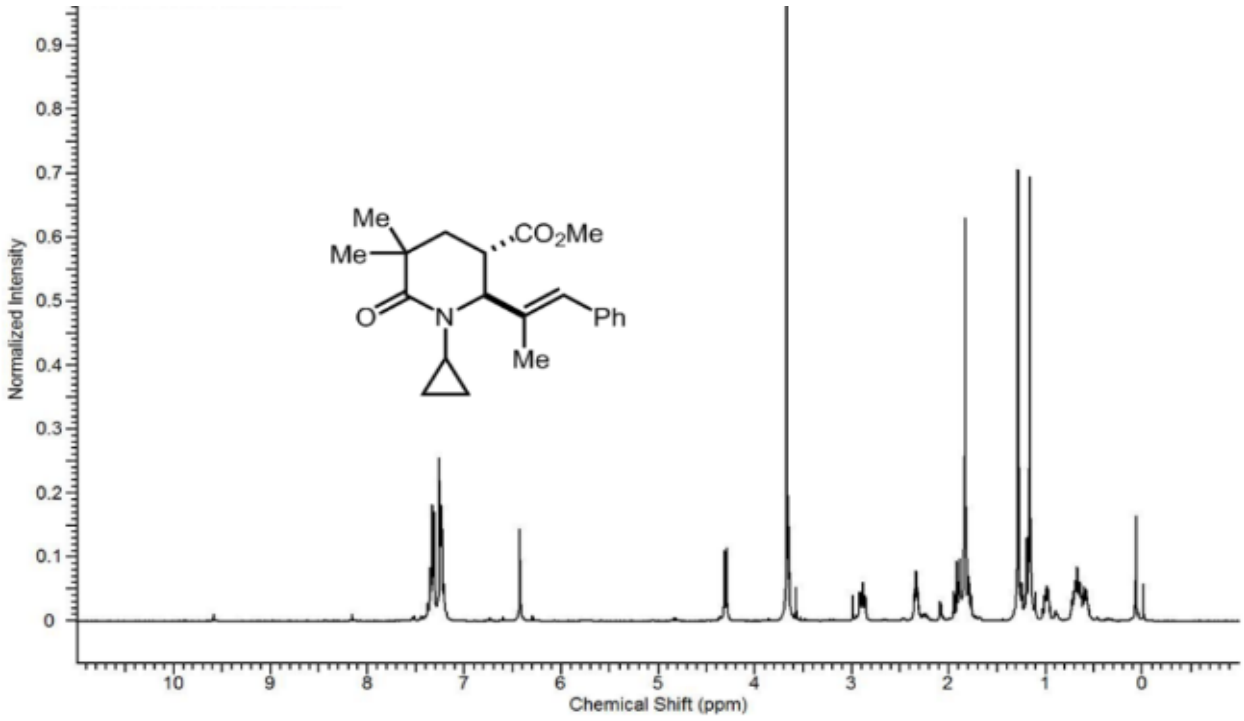
Spectrum 1-**213**: DEPT-135 NMR spectrum of **7m2.**



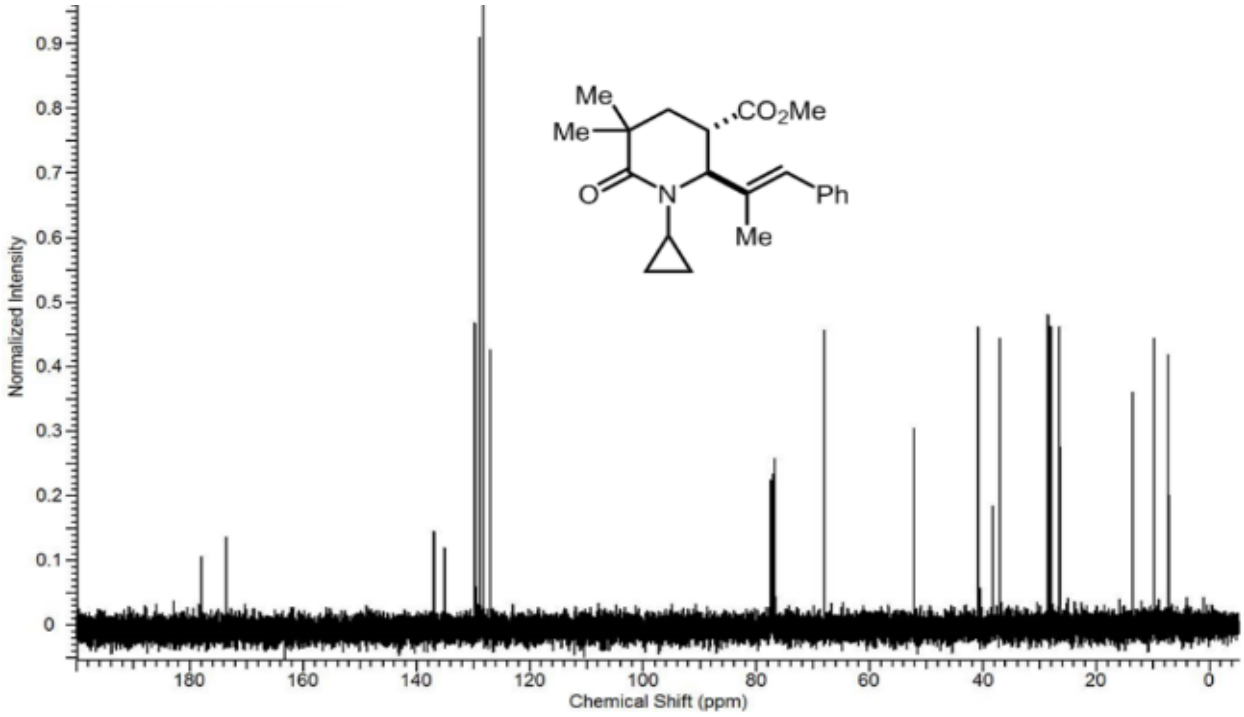
Spectrum 1-**214**: GC spectrum of **7n2.**



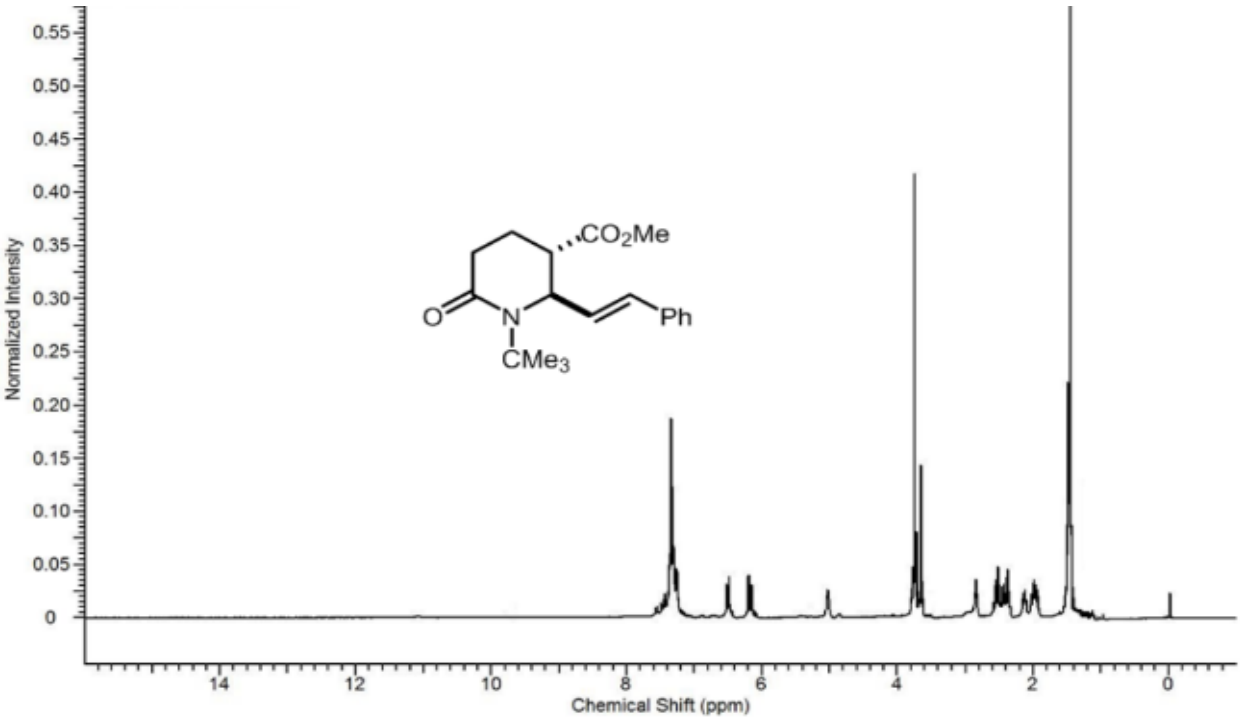
Spectrum 1-**215**: MS spectrum of **7n2.**



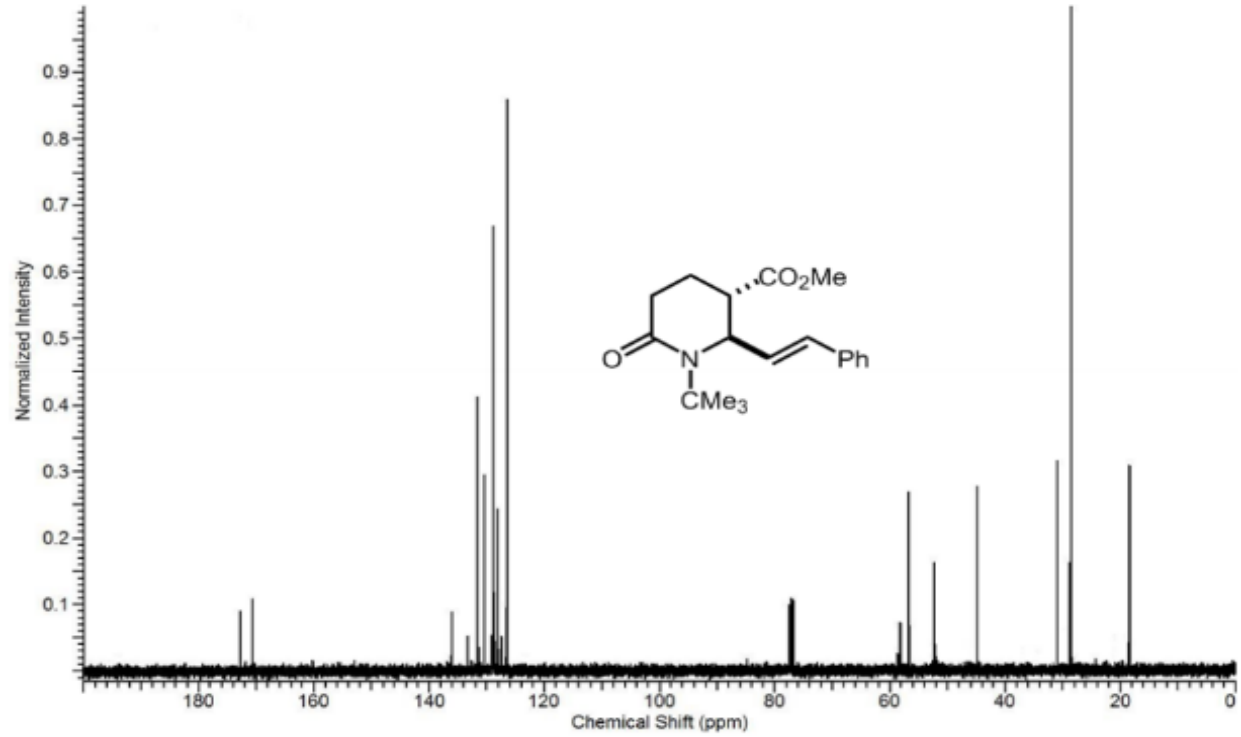
Spectrum 1-**216**: ^{1}H NMR spectrum of **7n2.**



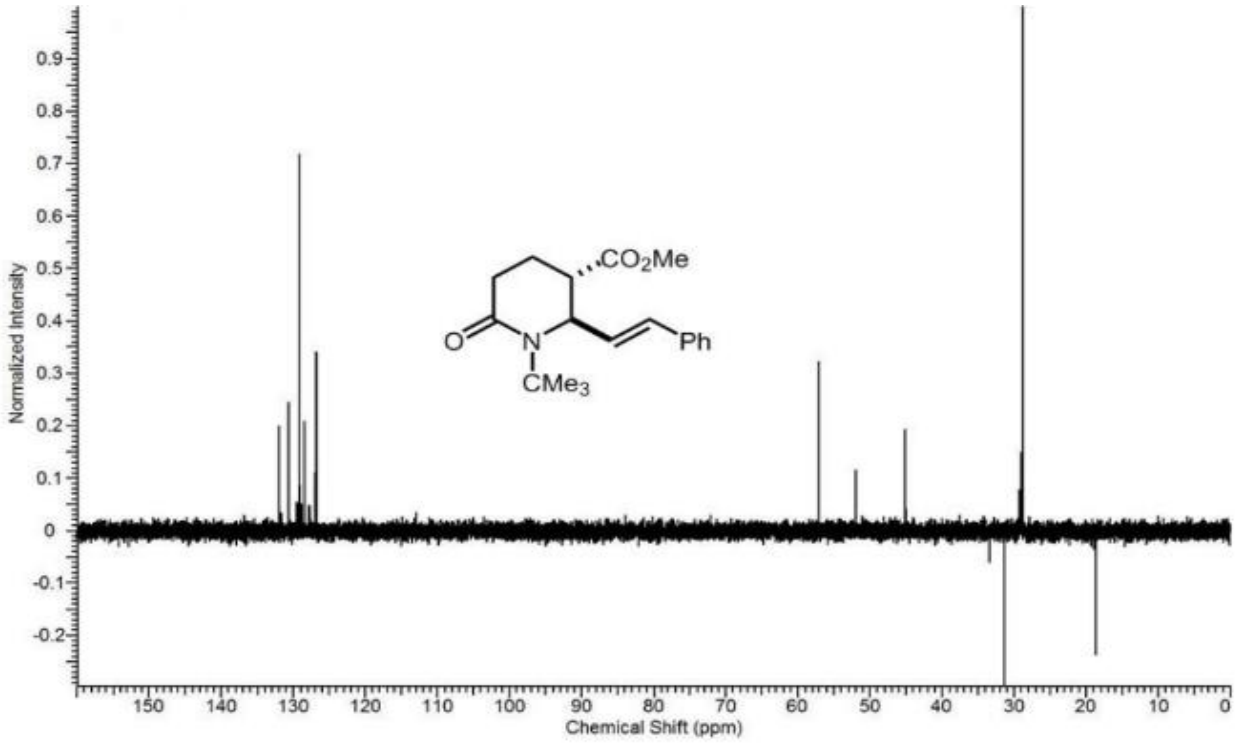
Spectrum 1-**217**: ^{13}C NMR spectrum of **7n2.**



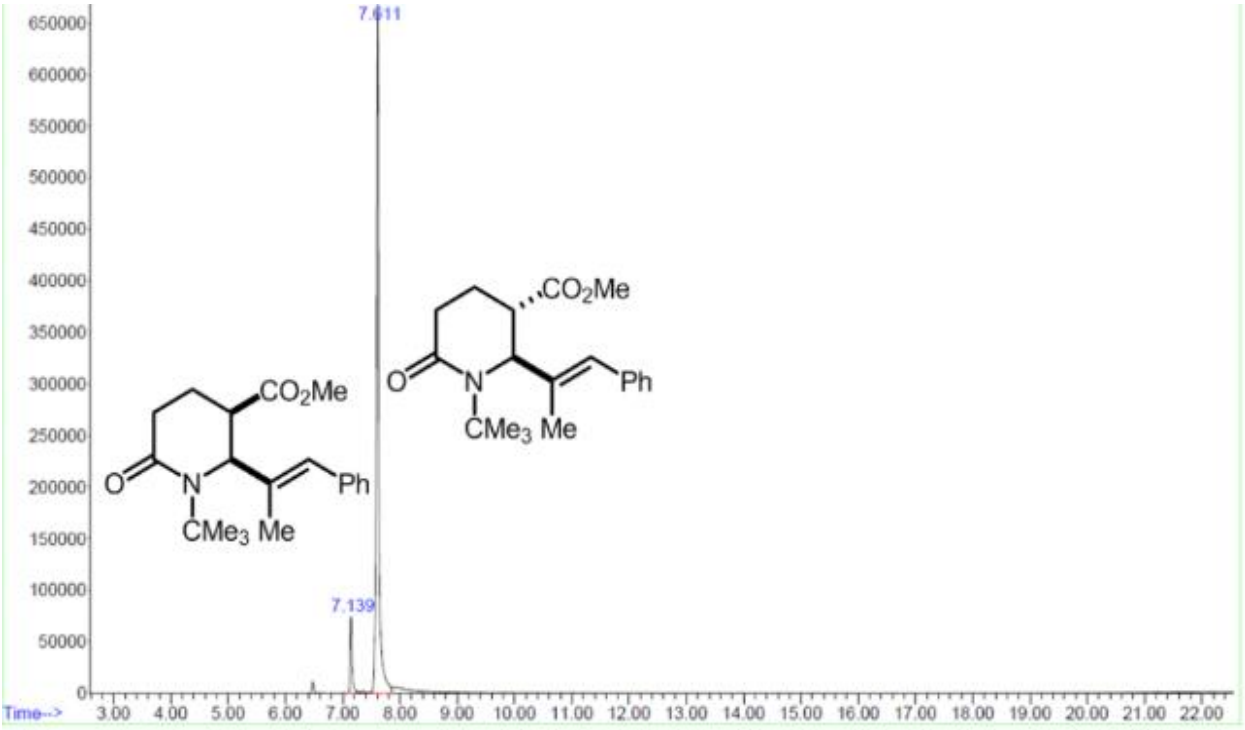
Spectrum 1-**218**: ^{1}H NMR spectrum of **7o2.**



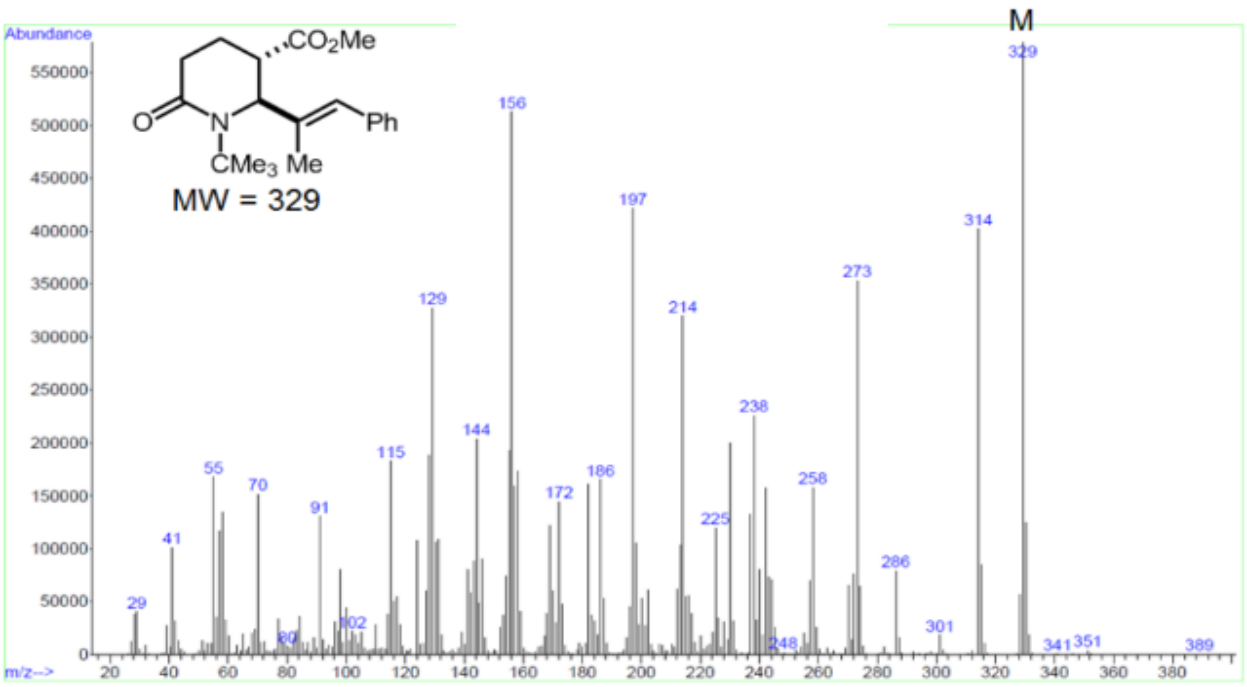
Spectrum 1-**219**: ^{13}C NMR spectrum of **7o2.**



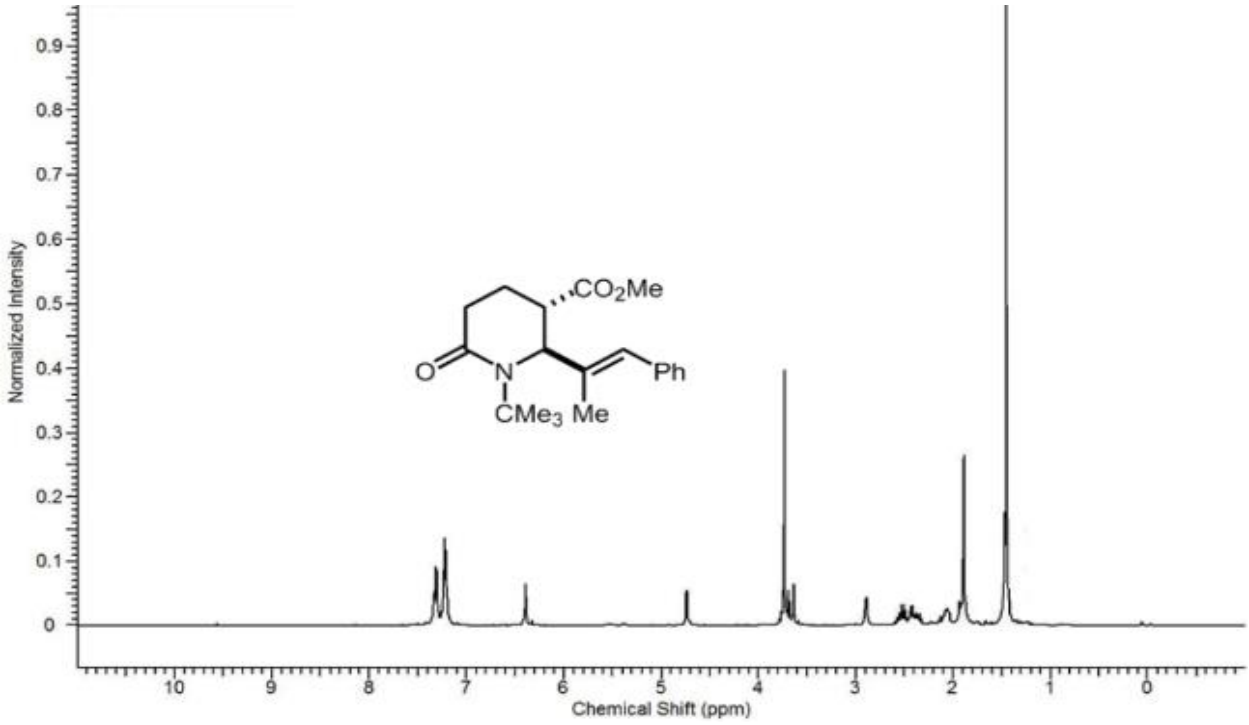
Spectrum 1-**220**: DEPT-135 NMR spectrum of **7o2.**



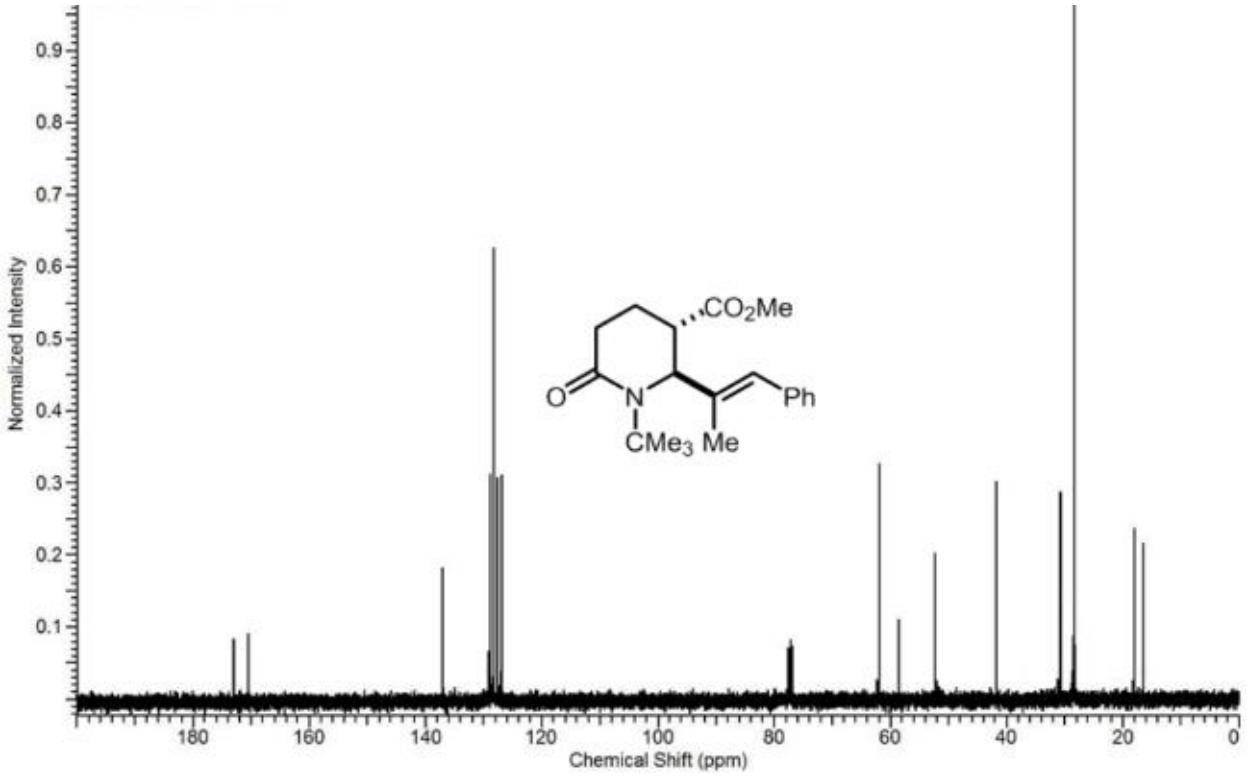
Spectrum 1-22**1**: GC spectrum of **7p2.**



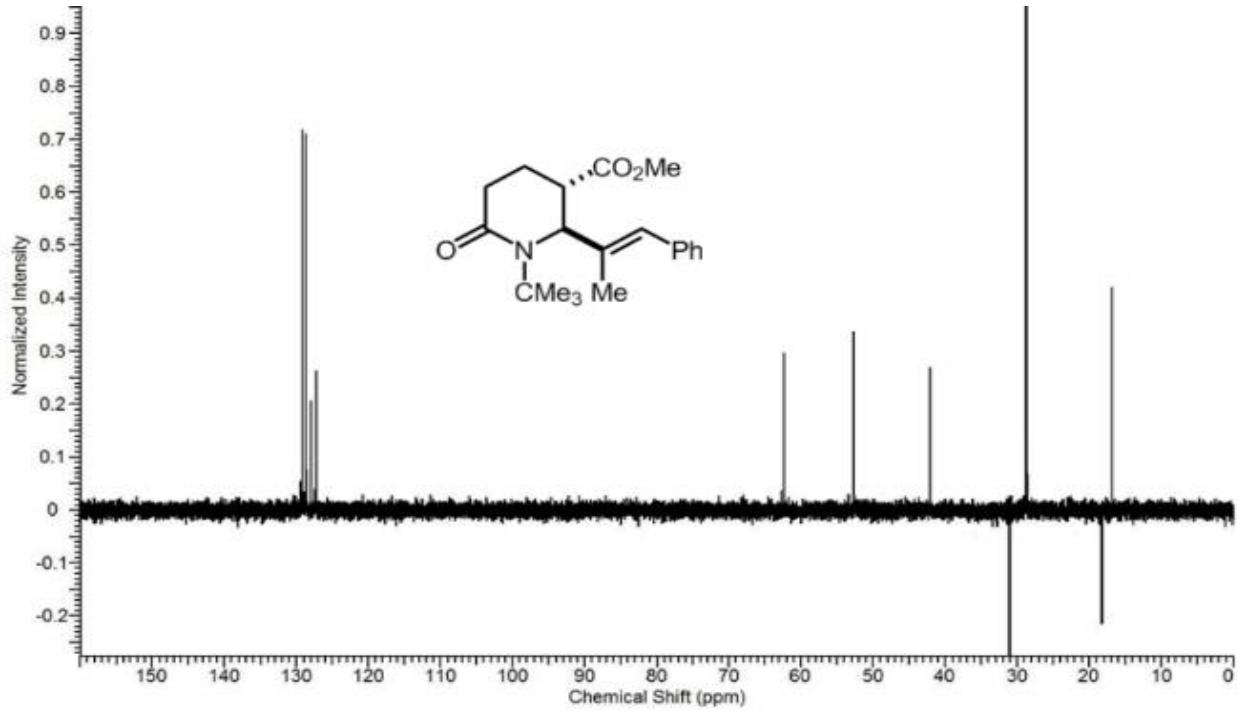
Spectrum 1-**222**: MS spectrum of **7p2.**



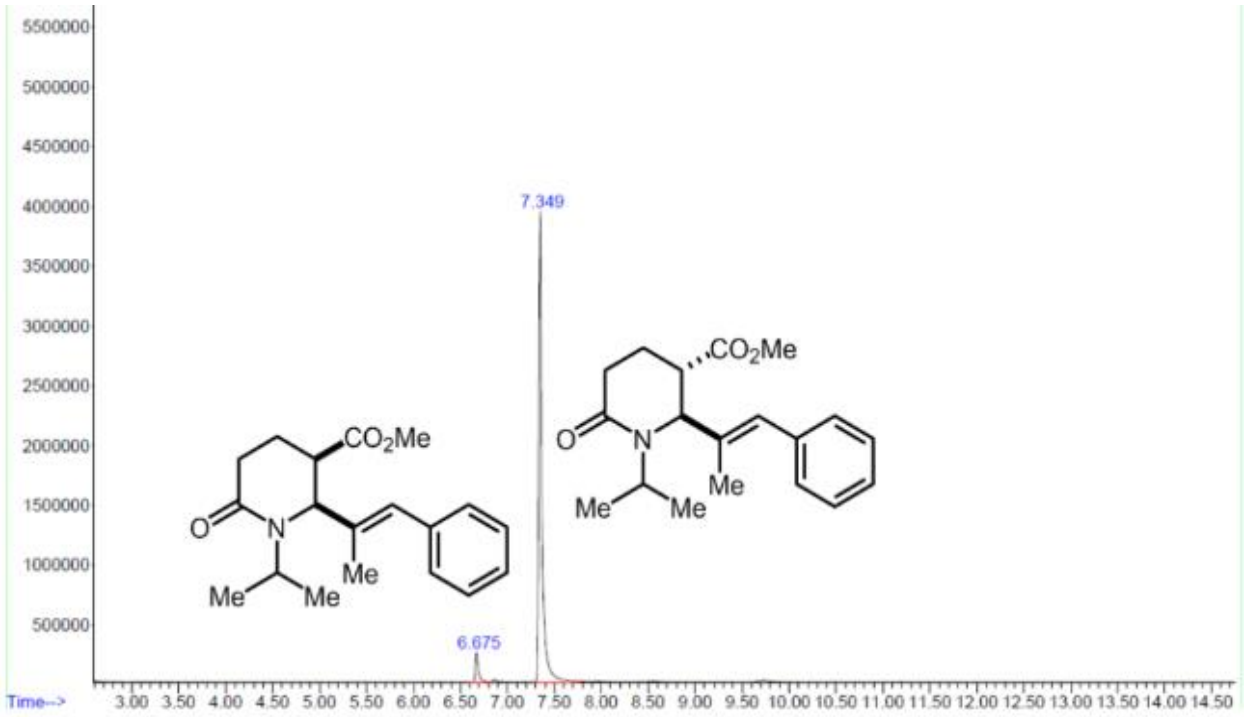
Spectrum 1-**223**: ^{1}H NMR spectrum of **7p2.**



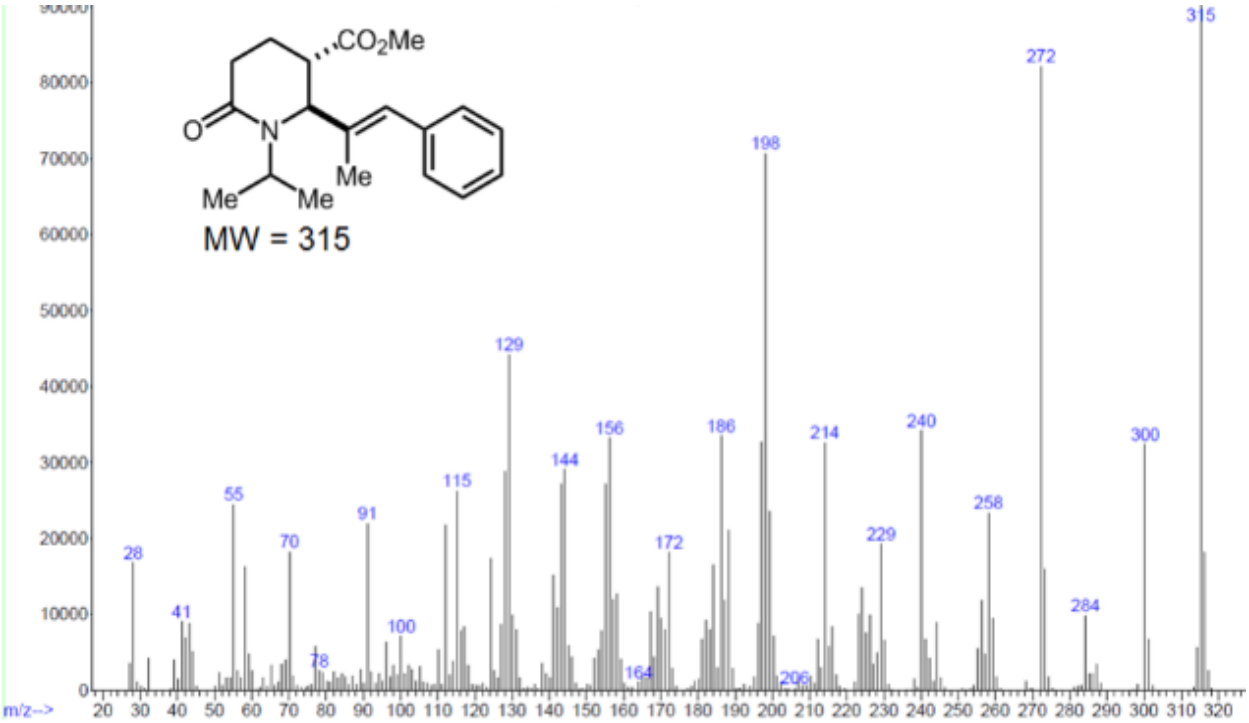
Spectrum 1-**224**: ^{13}C NMR spectrum of **7p2.**



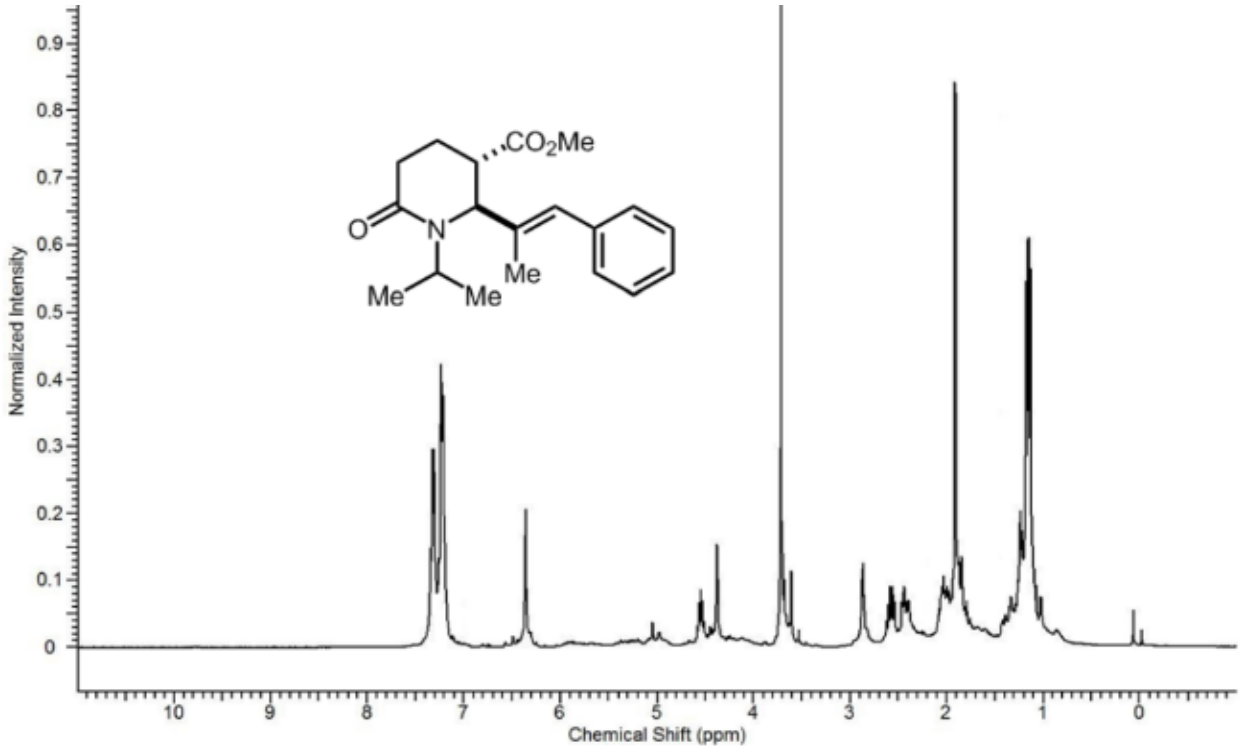
Spectrum 1-**225**: DEPT-135 NMR spectrum of **7p2.**



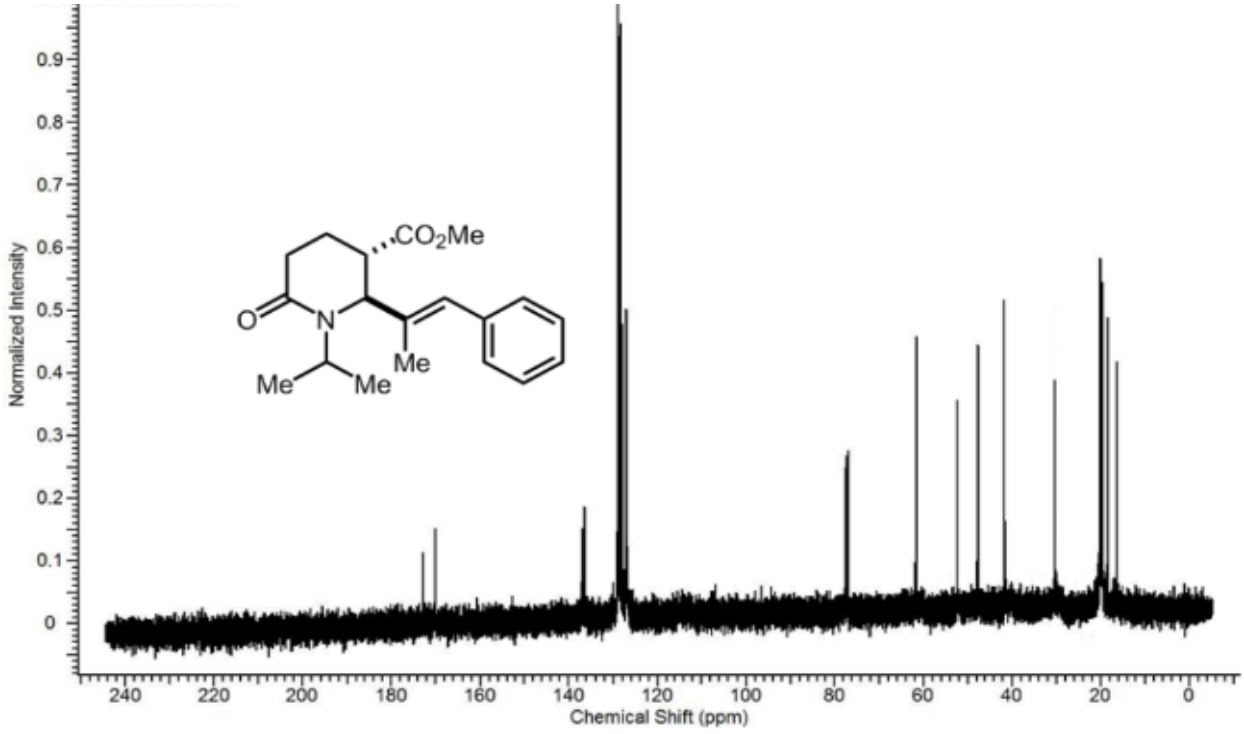
Spectrum 1-**226**: GC spectrum of **7q2.**



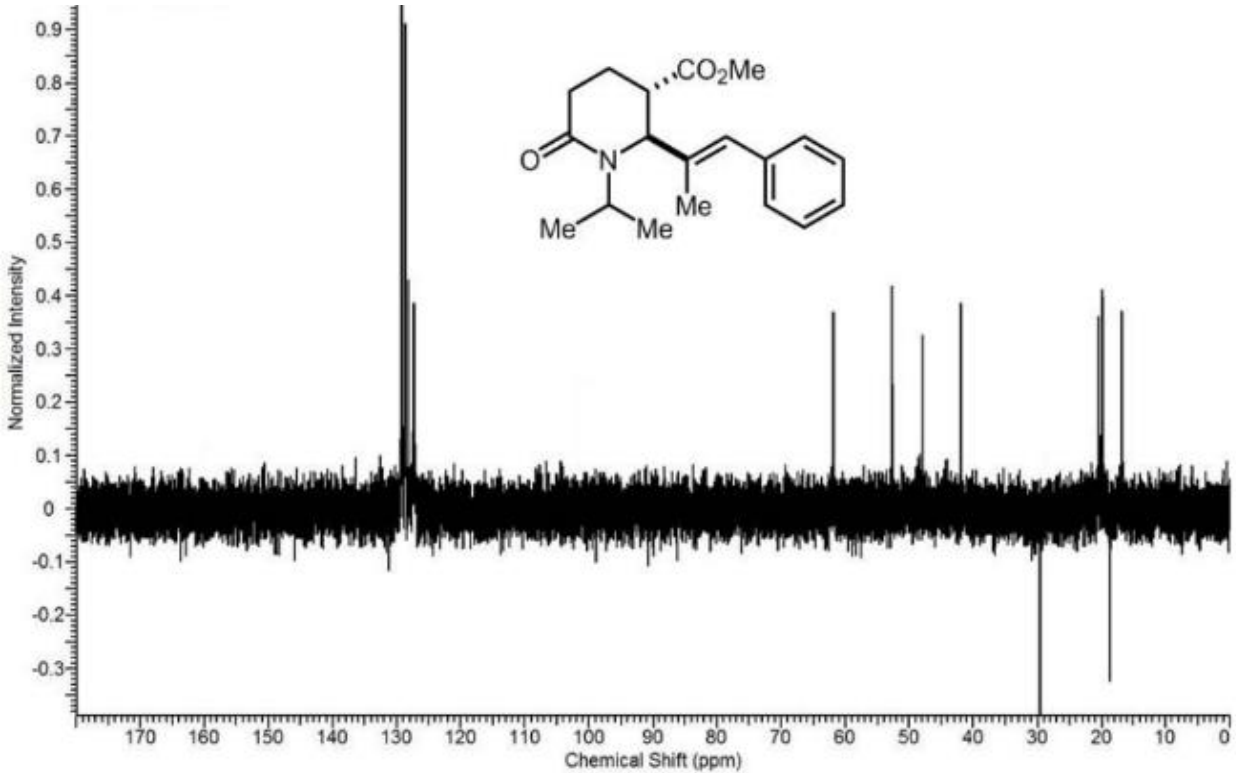
Spectrum 1-**227**: MS spectrum of **7q2.**



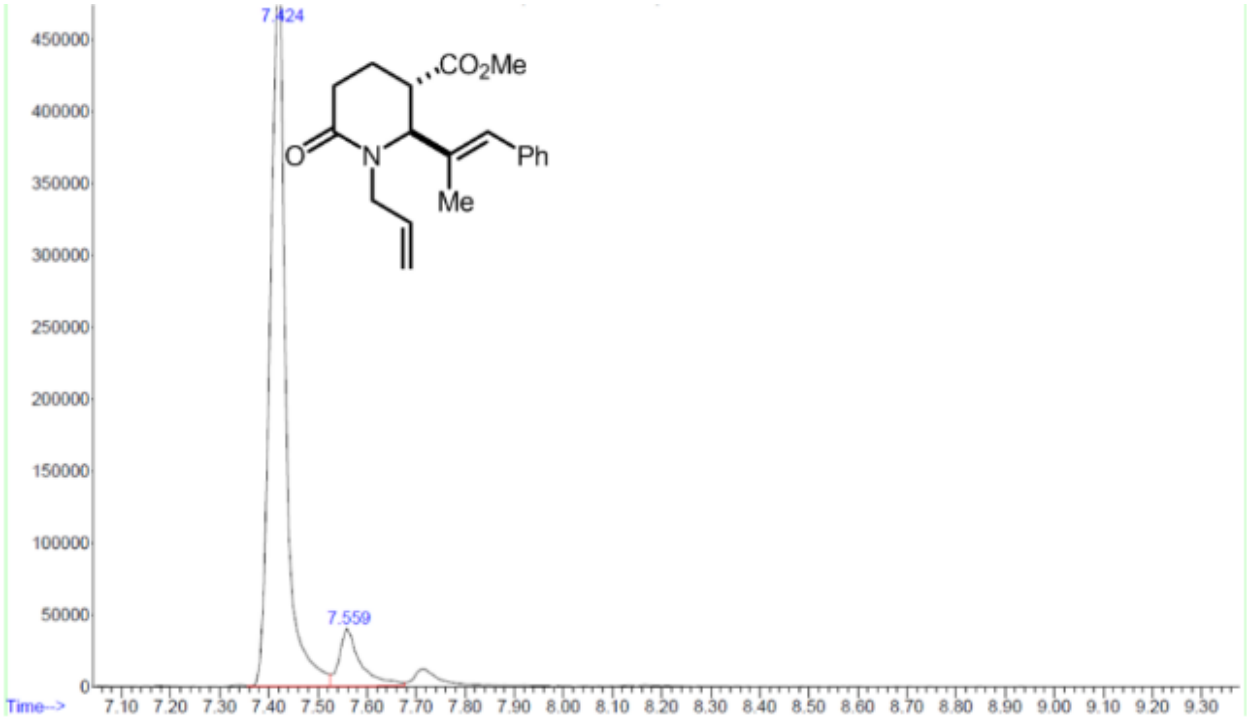
Spectrum 1-**228**: ^{1}H NMR spectrum of **7q2.**



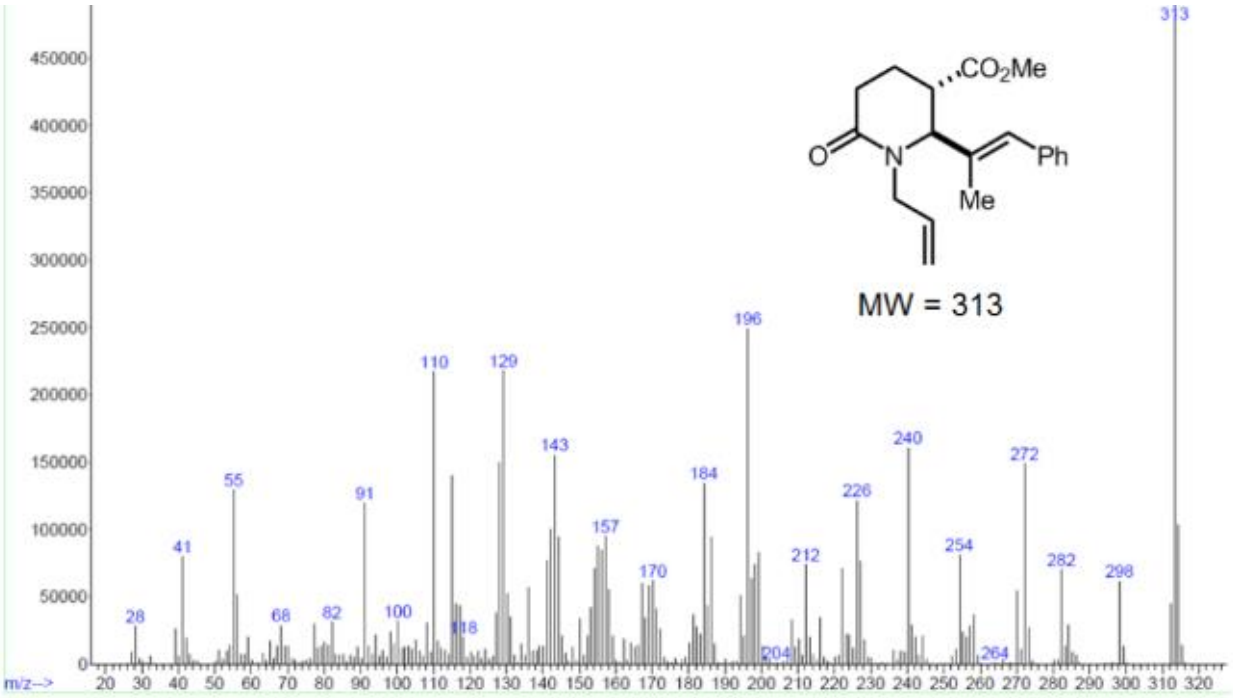
Spectrum 1-**229**: ^{13}C NMR spectrum of **7q2.**



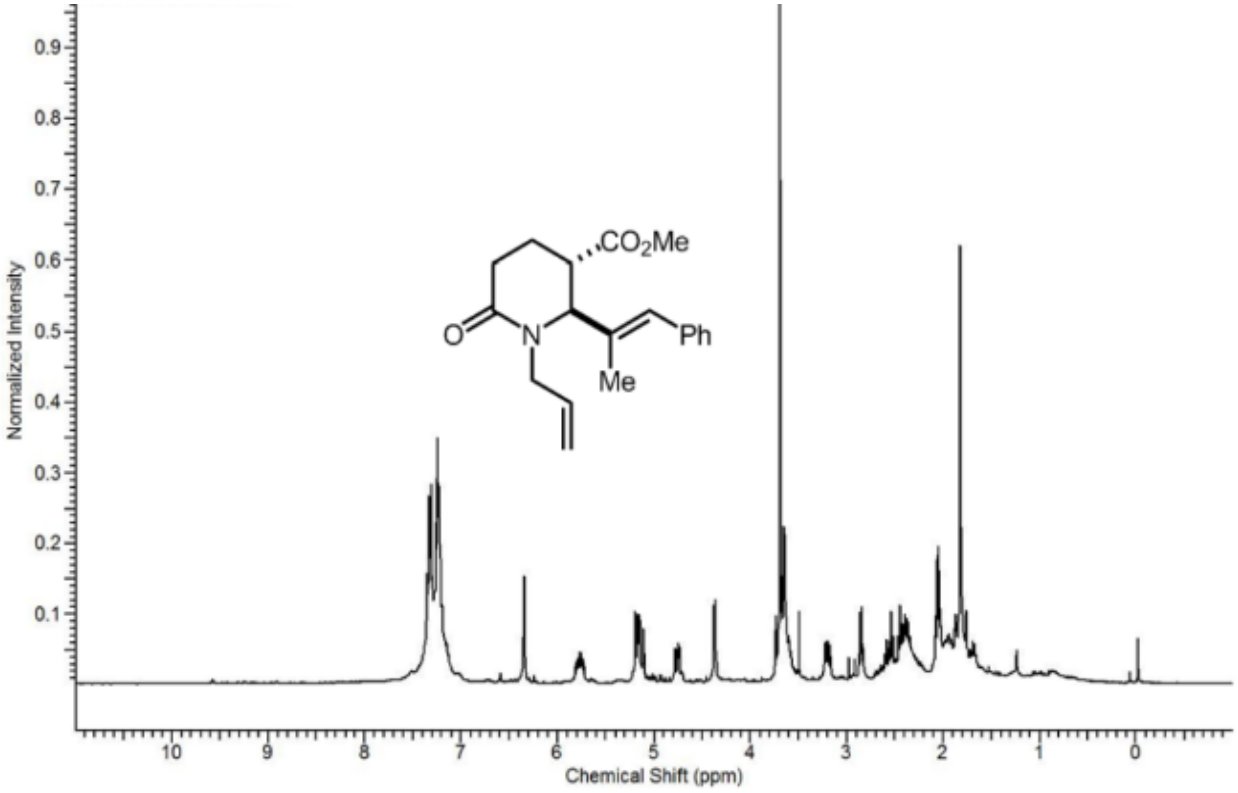
Spectrum 1-**230**: DEPT-135 NMR spectrum of **7q2.**



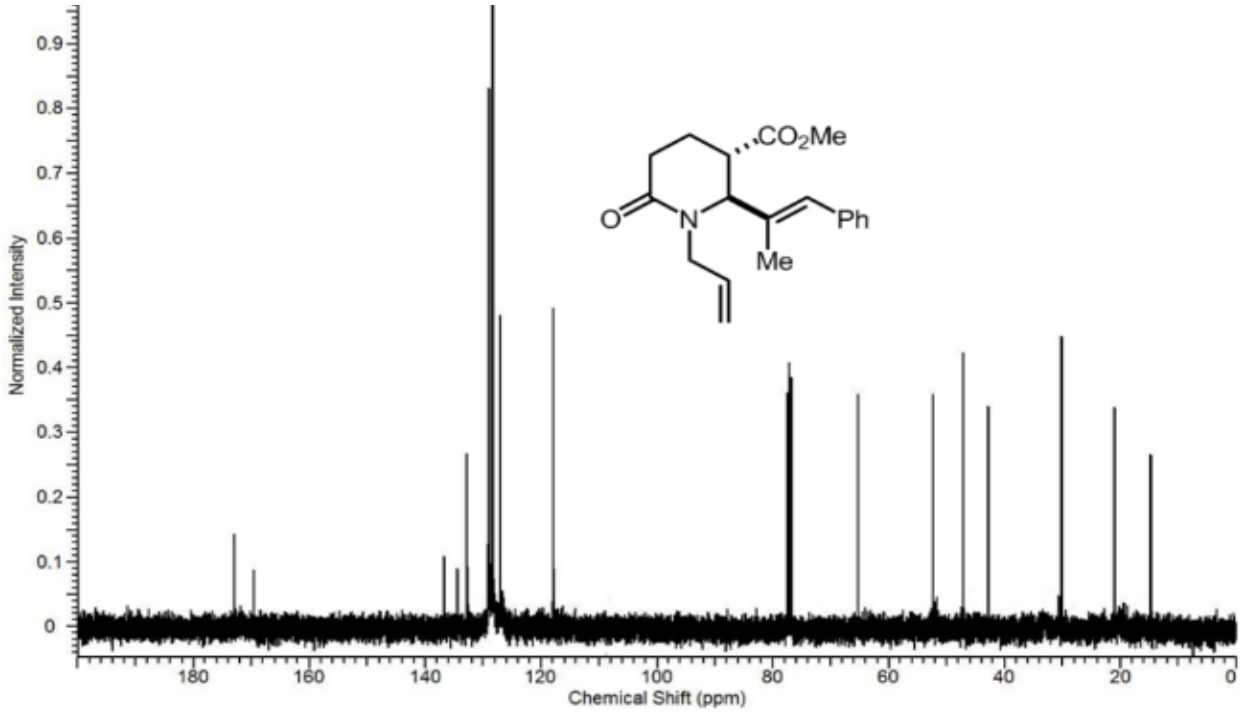
Spectrum 1-**231**: GC spectrum of **7r2.**



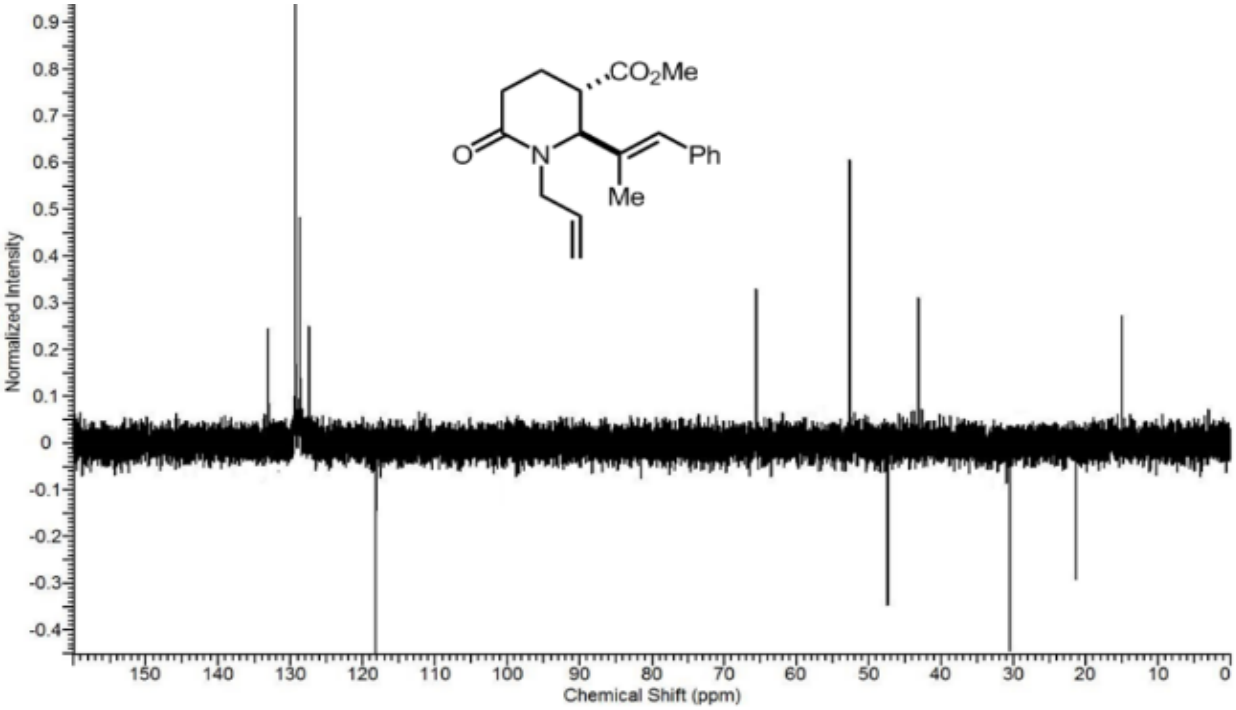
Spectrum 1-**232**: MS spectrum of **4r2**.



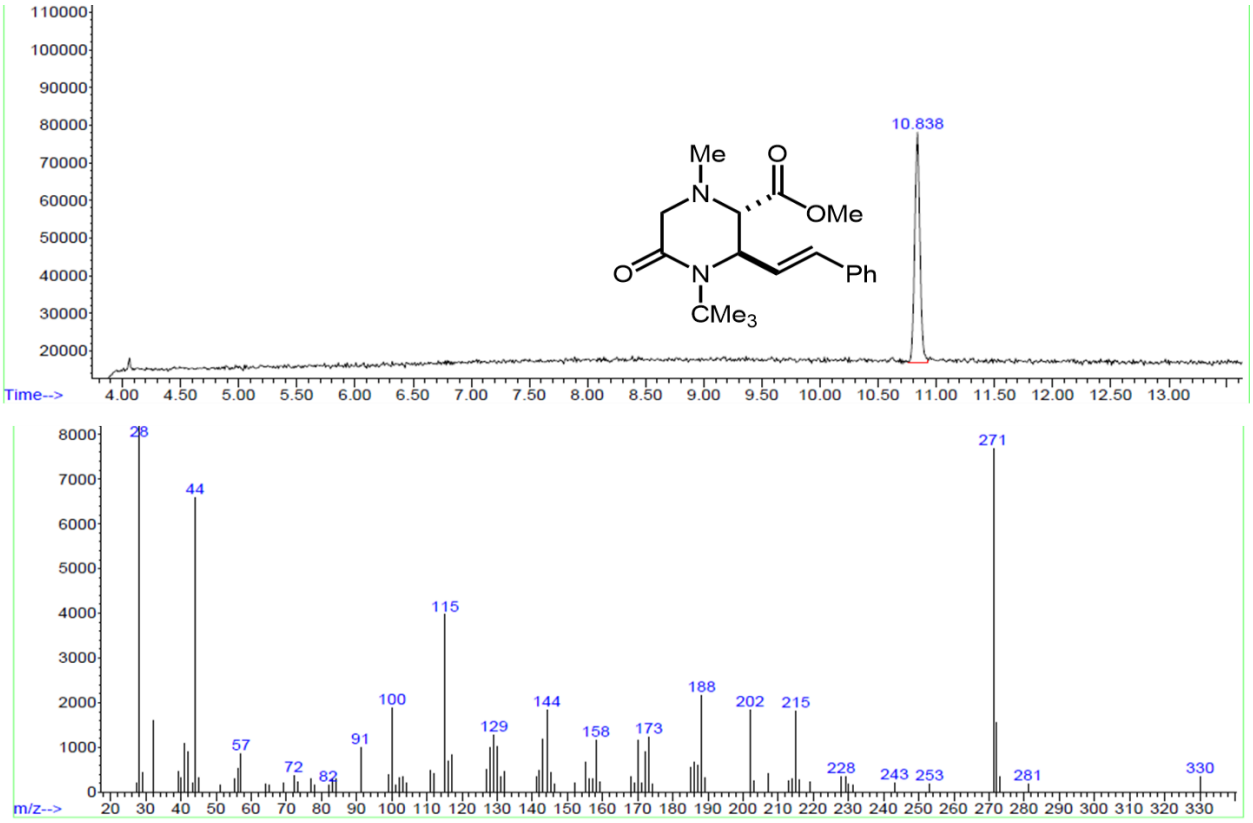
Spectrum 1-**233**: ^{1}H NMR spectrum of **7r2.**



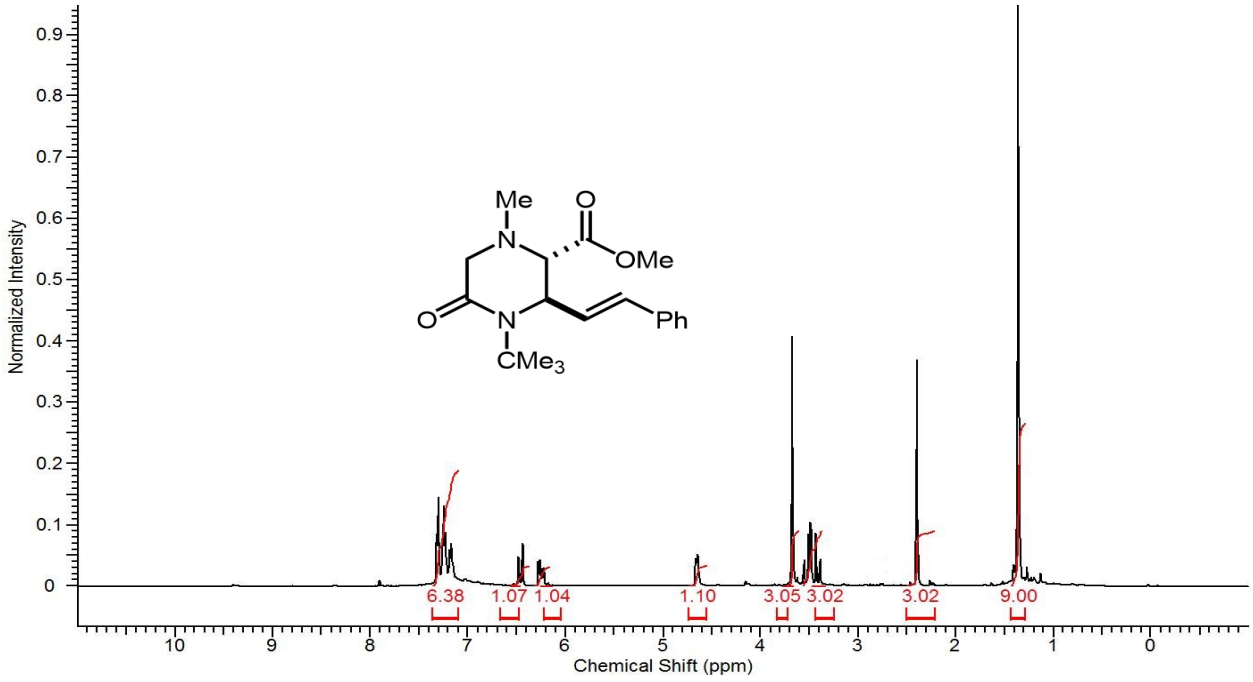
Spectrum 1-**234**: ^{13}C NMR spectrum of **7r2.**



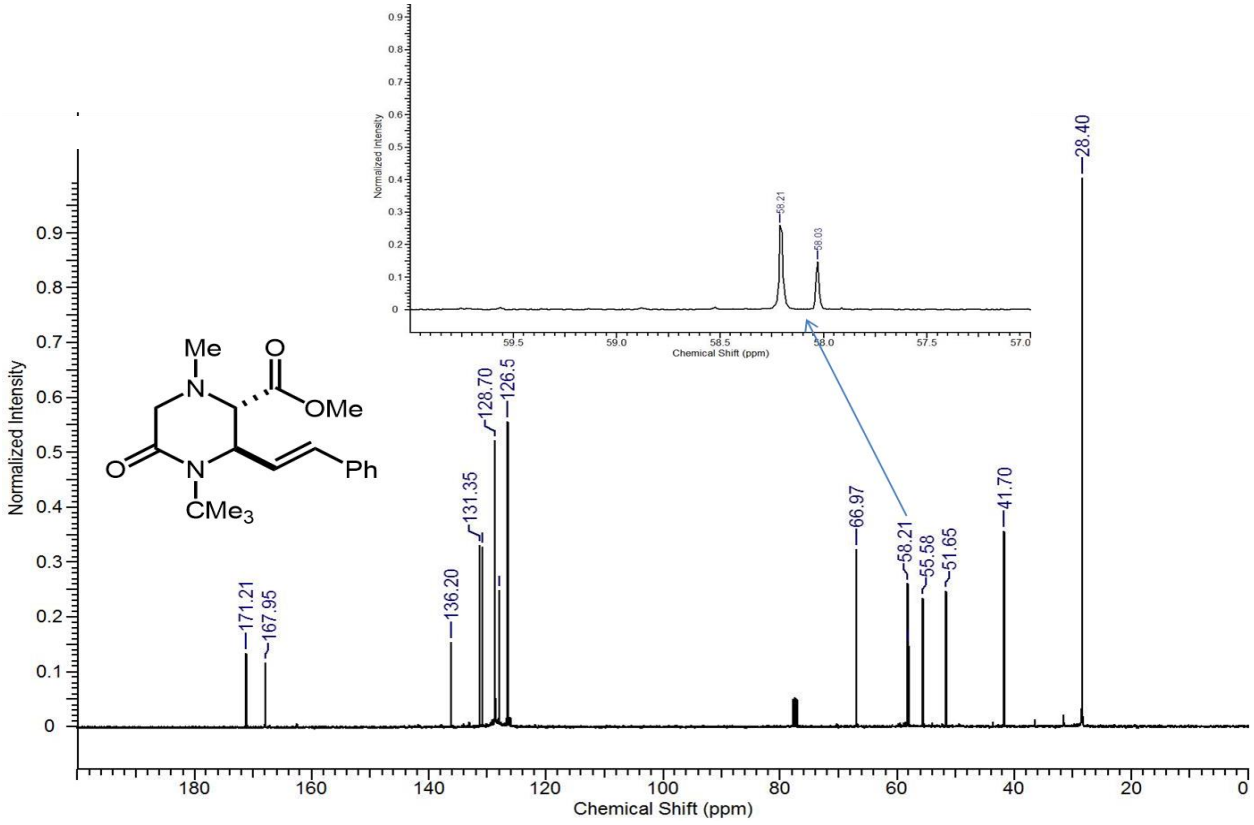
Spectrum 1-**235**: DEPT-135 NMR spectrum of 7r**2.**



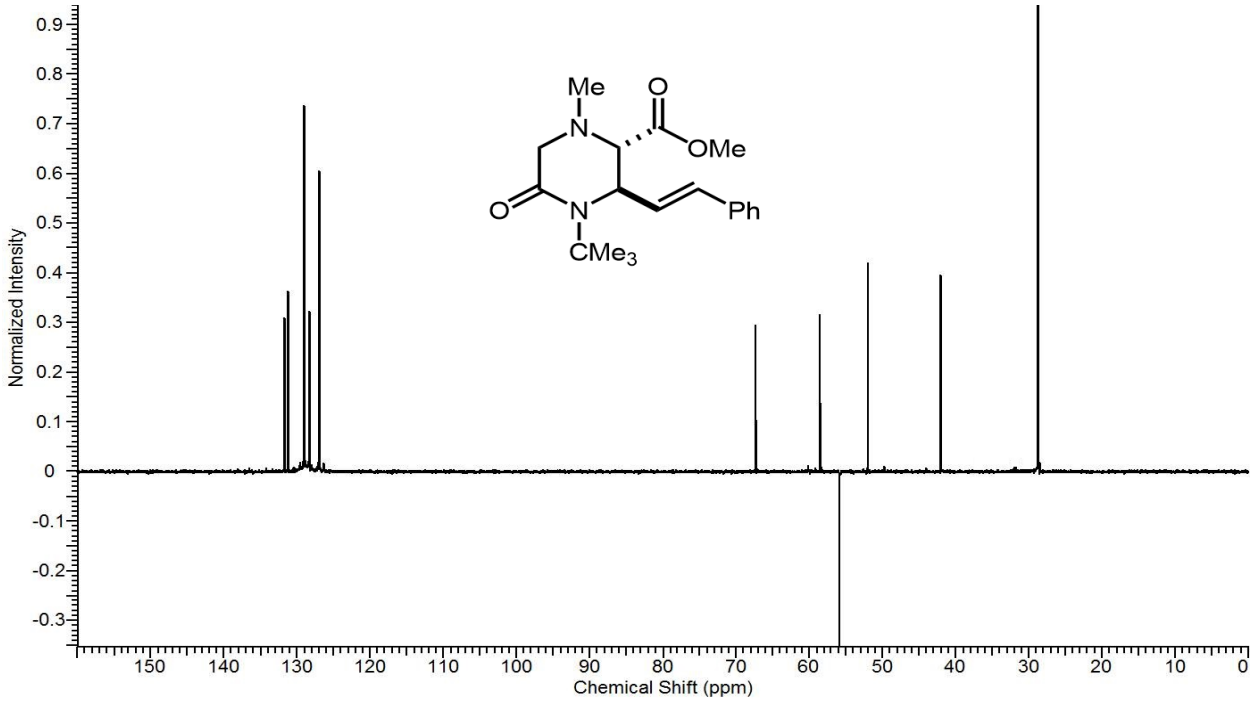
Spectrum 1-**236 and 1-237**: GC and MS spectra of **8a2.**



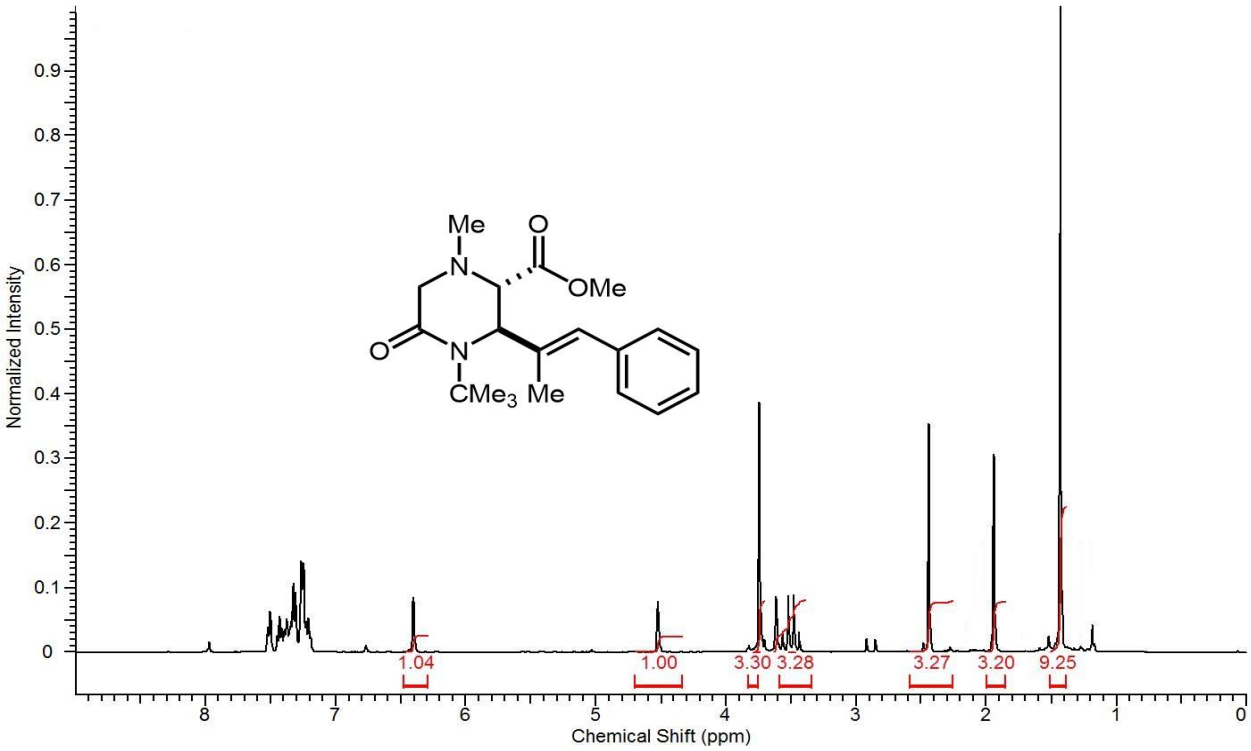
Spectrum 1-**238**: ^{1}H NMR spectrum of **8a2.**



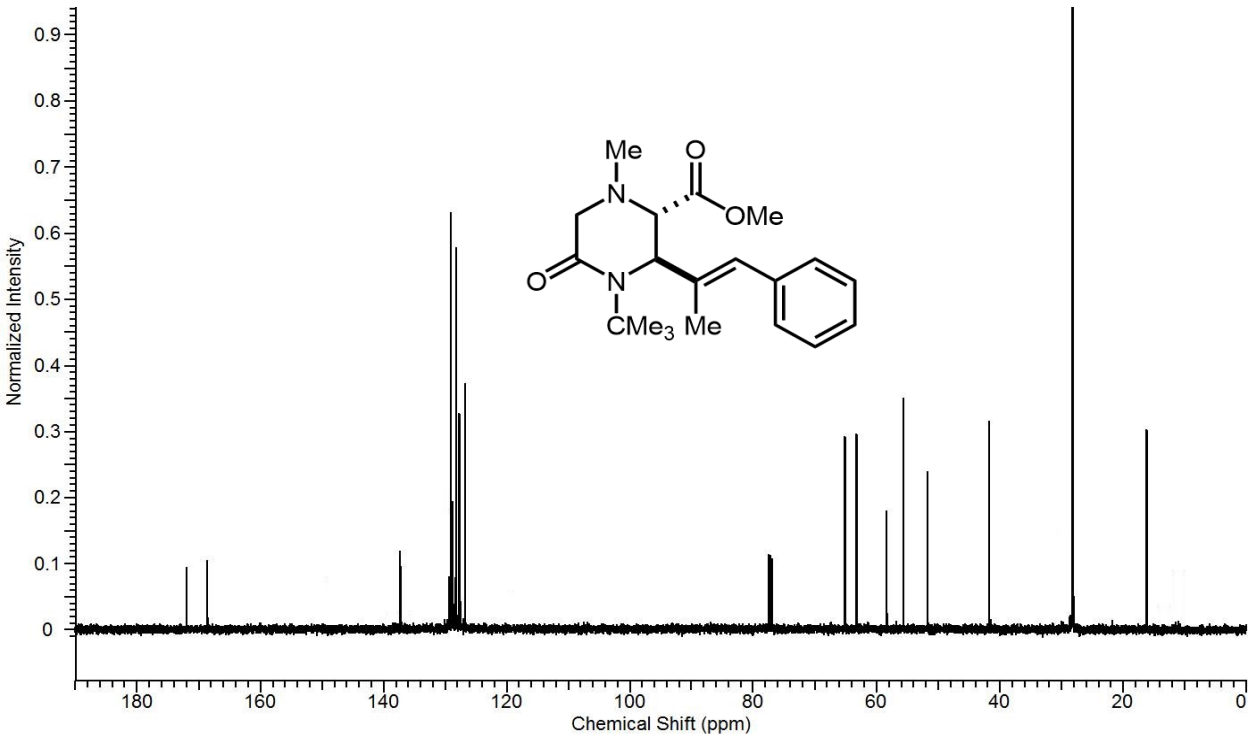
Spectrum 1-**239**: ^{13}C NMR spectrum of **8a2** (zoomed-in spectrum included).



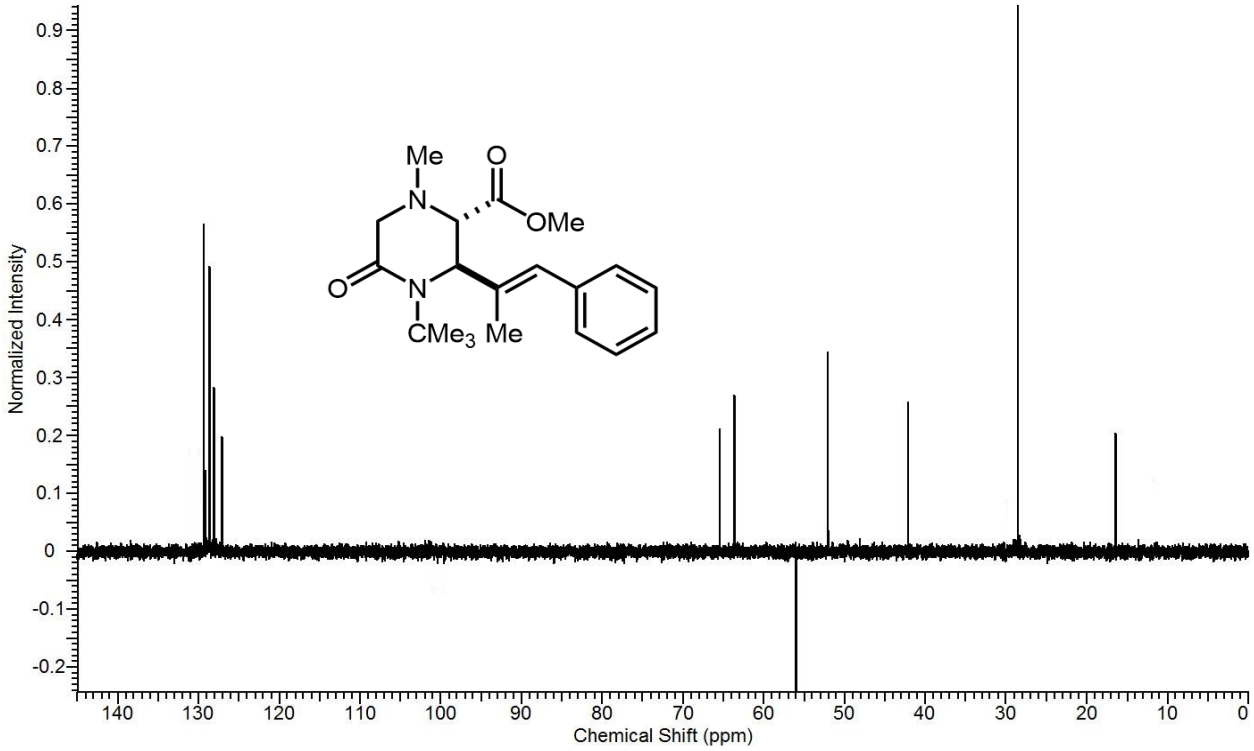
Spectrum 1-**240**: DEPT-135 NMR spectrum of **8a2.**



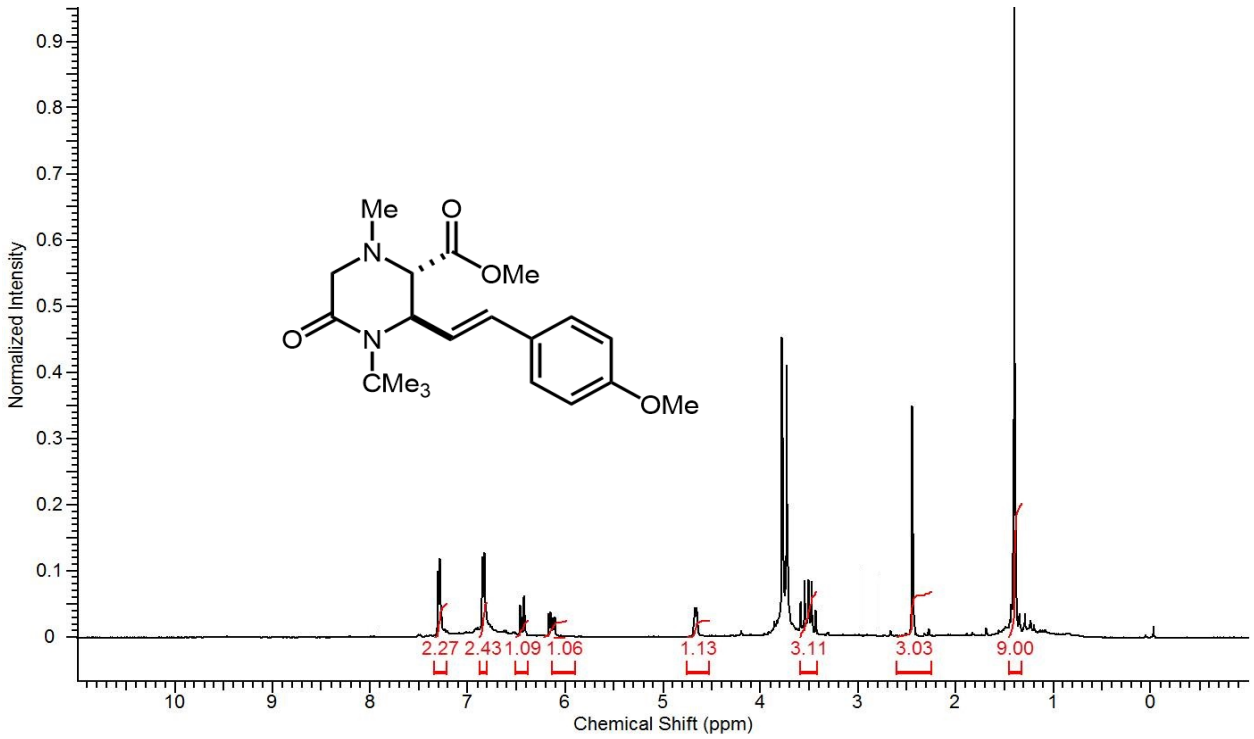
Spectrum 1-**241**: ^{1}H NMR spectrum of **8b2.**



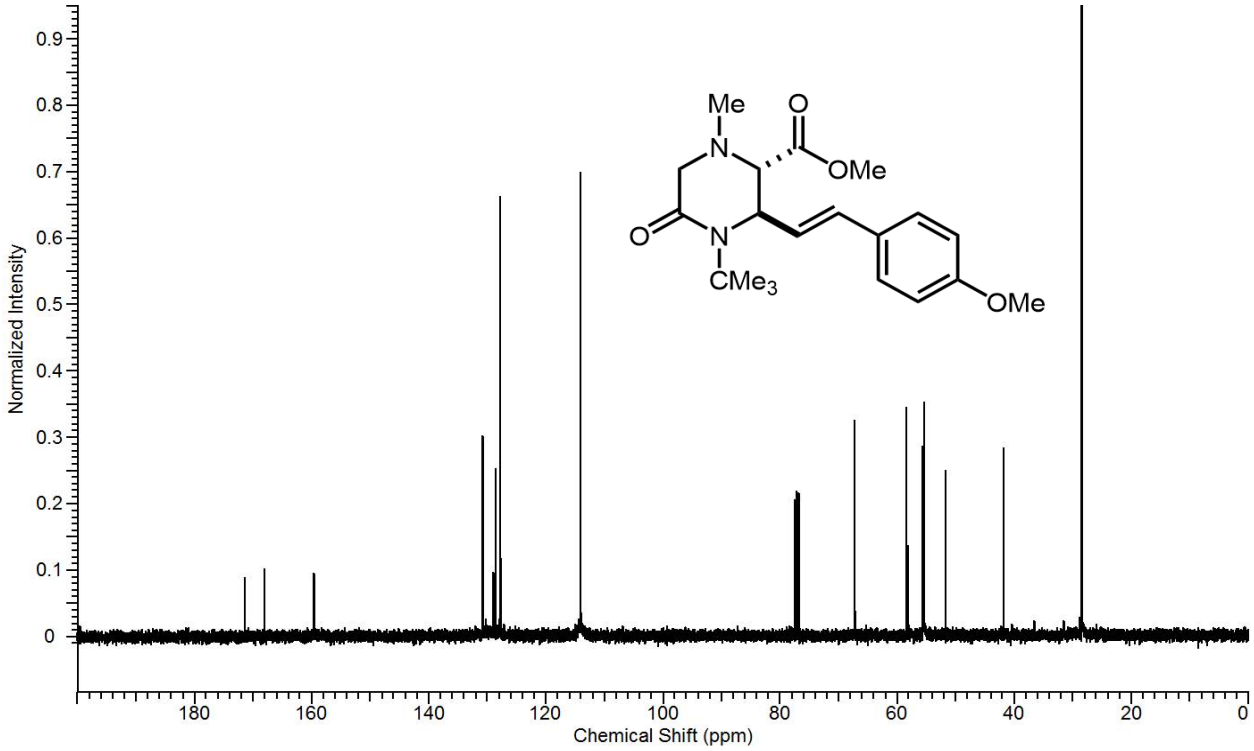
Spectrum 1-**242**: ^{13}C NMR spectrum of **8b2.**



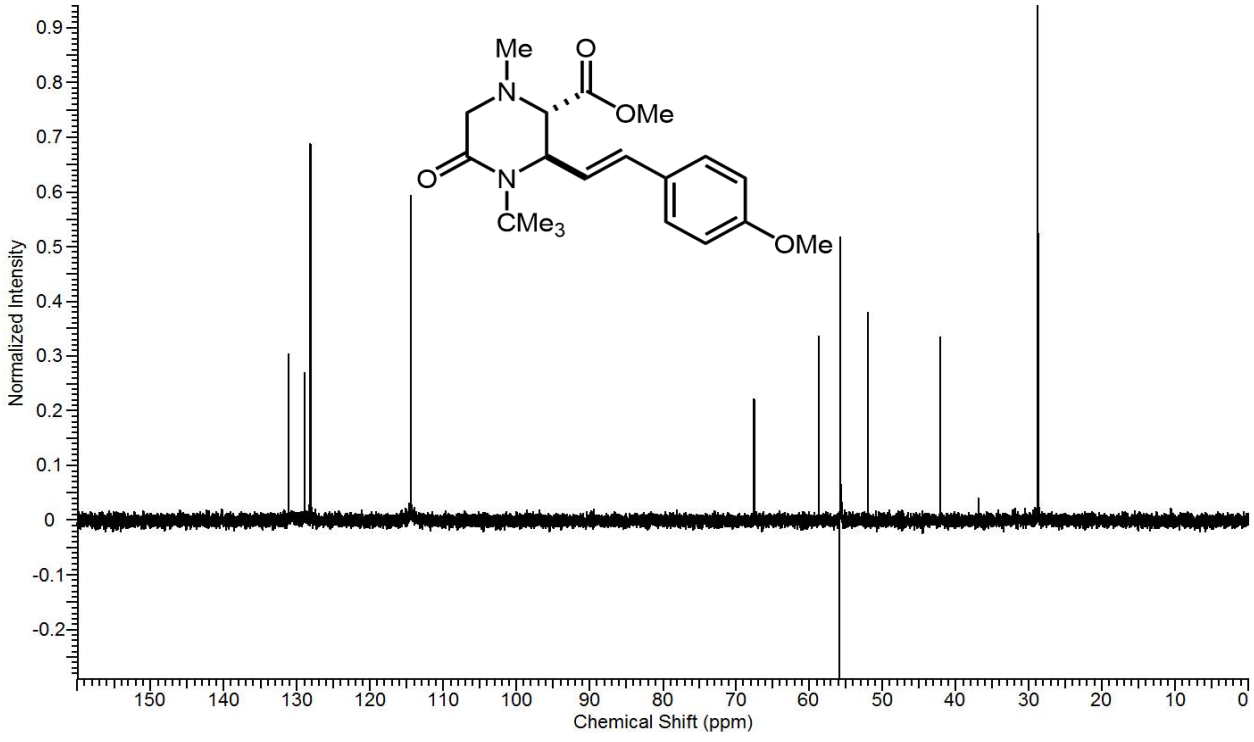
Spectrum 1-**243**: DEPT-135 NMR spectrum of **8b2.**



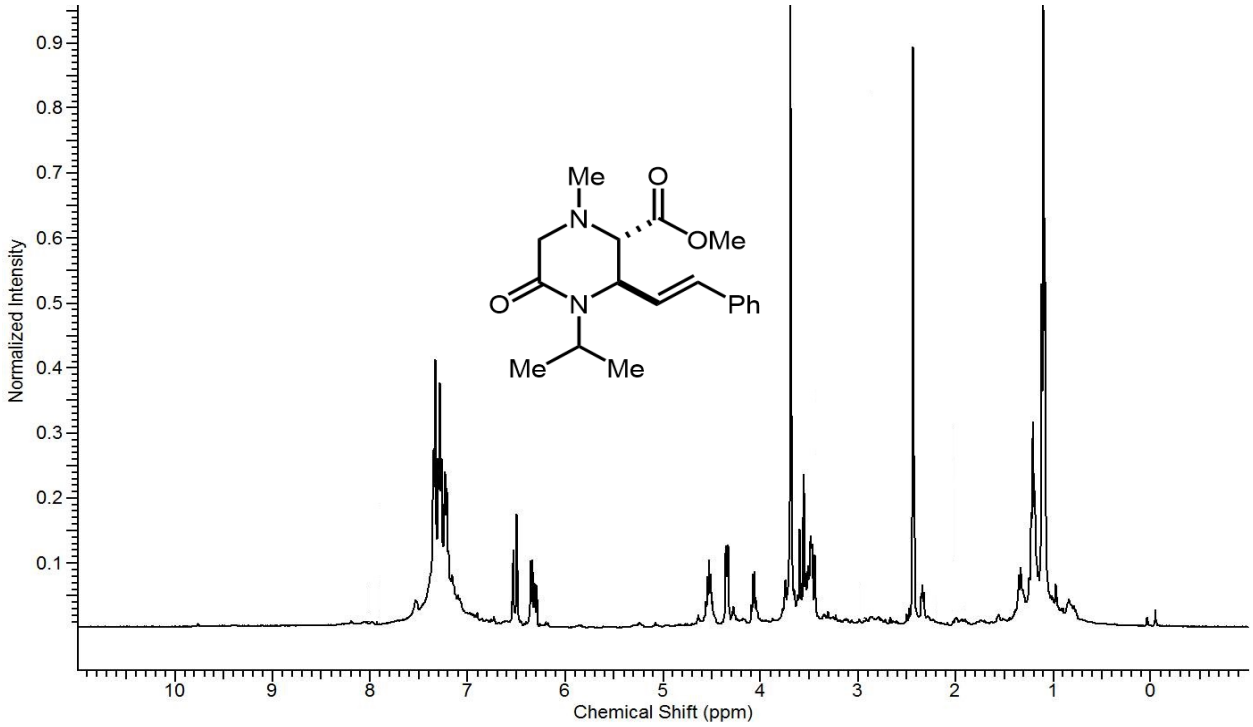
Spectrum 1-**244**: ^{1}H NMR spectrum of **8c2.**



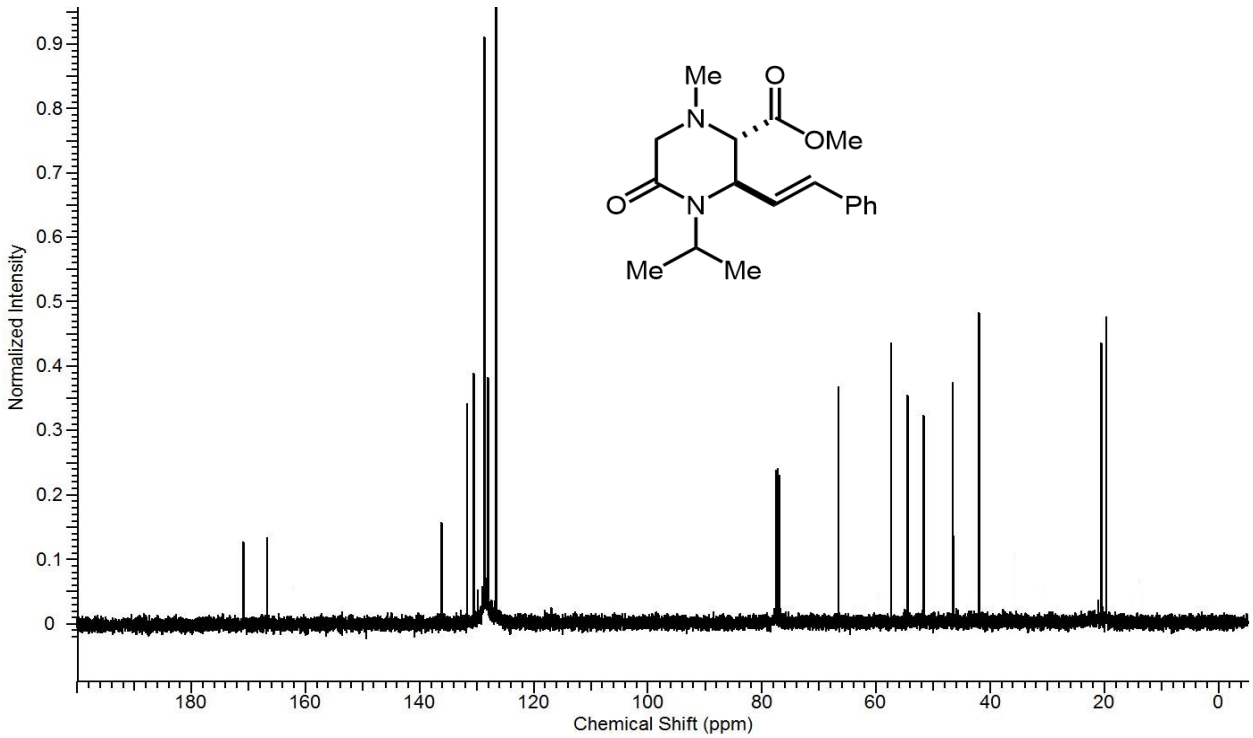
Spectrum 1-**245**: ^{13}C NMR spectrum of **8c2.**



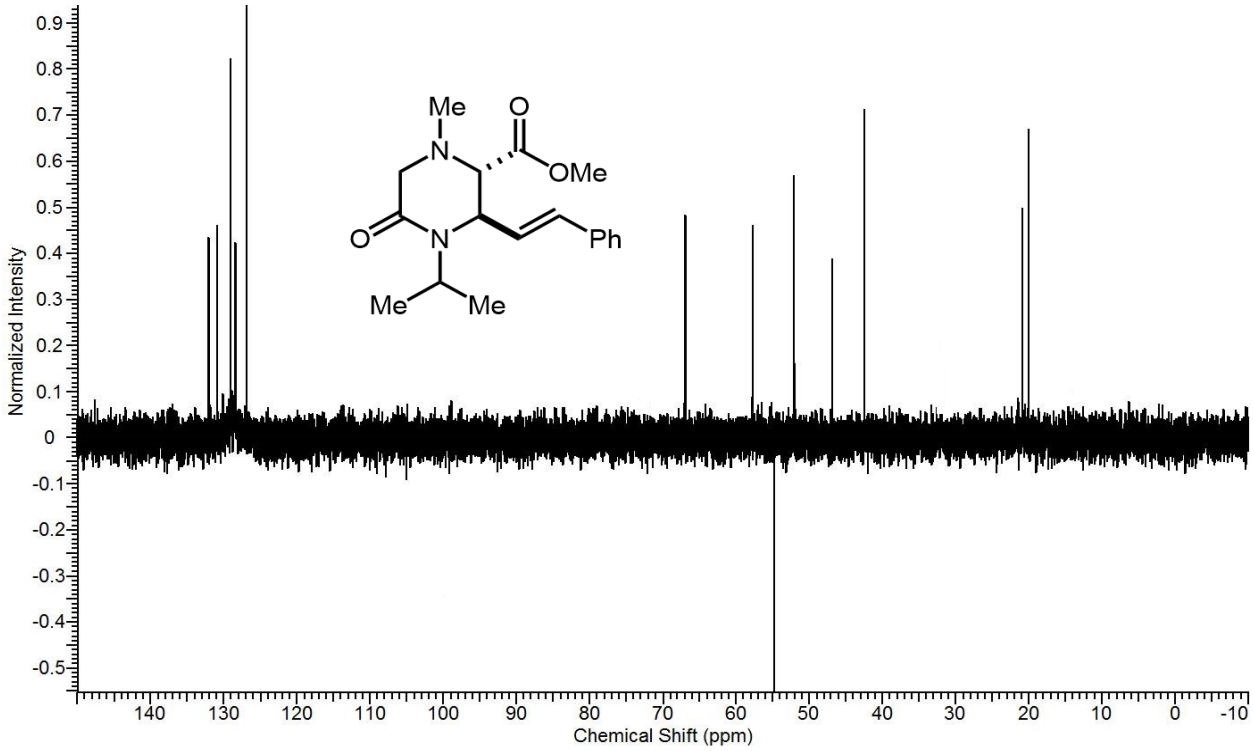
Spectrum 1-**246**: DEPT-135 NMR spectrum of **8c2.**



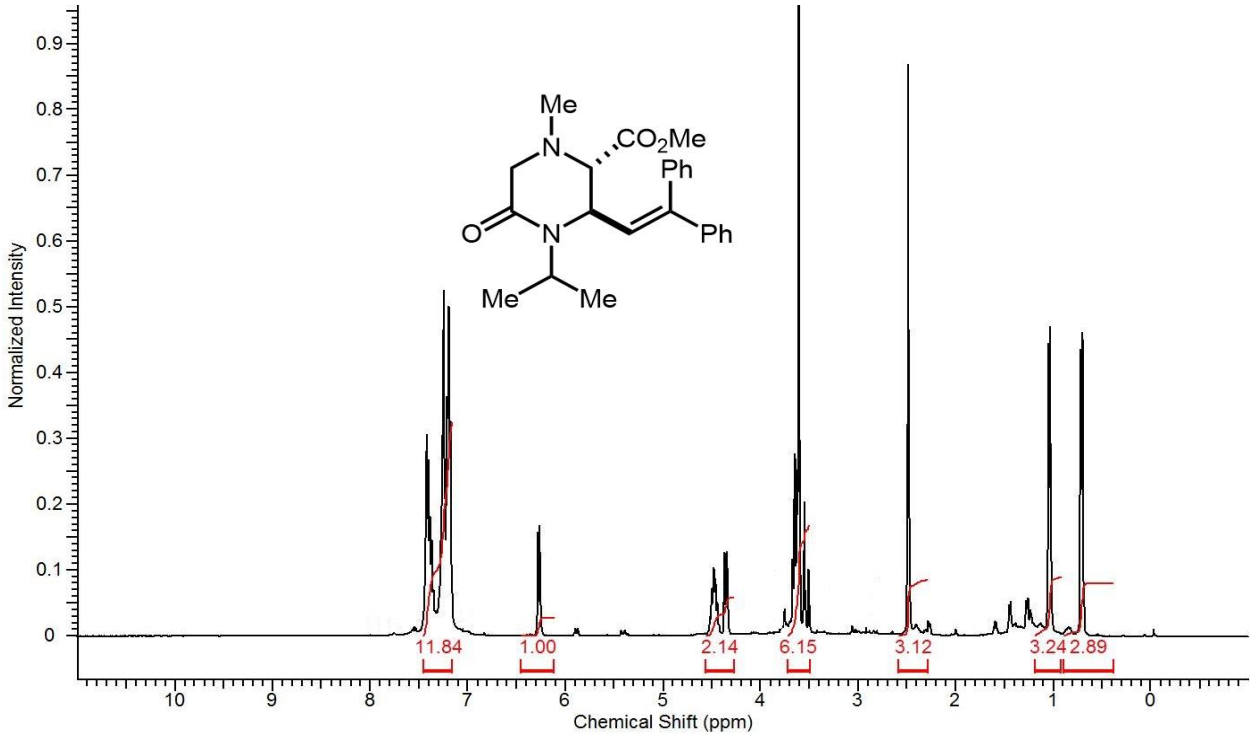
Spectrum 1-**247**: ^{1}H NMR spectrum of **8d2.**



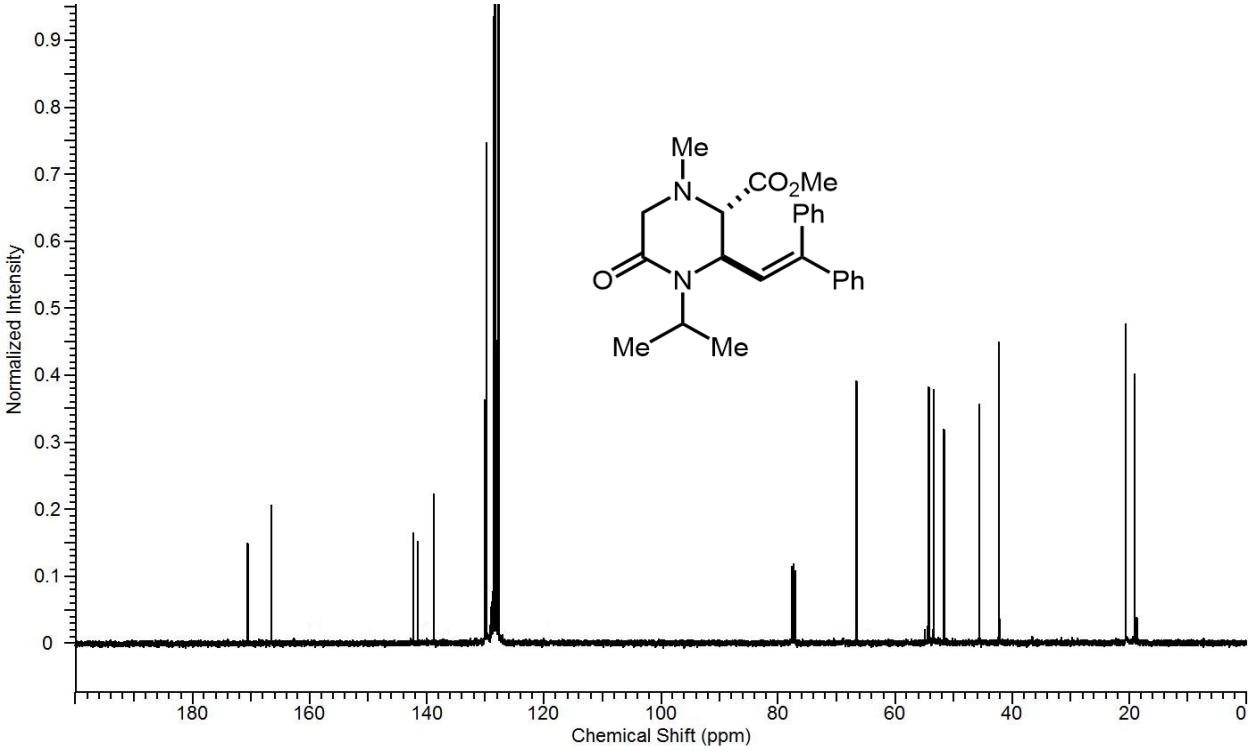
Spectrum 1-**248**: ^{13}C NMR spectrum of **8d2.**



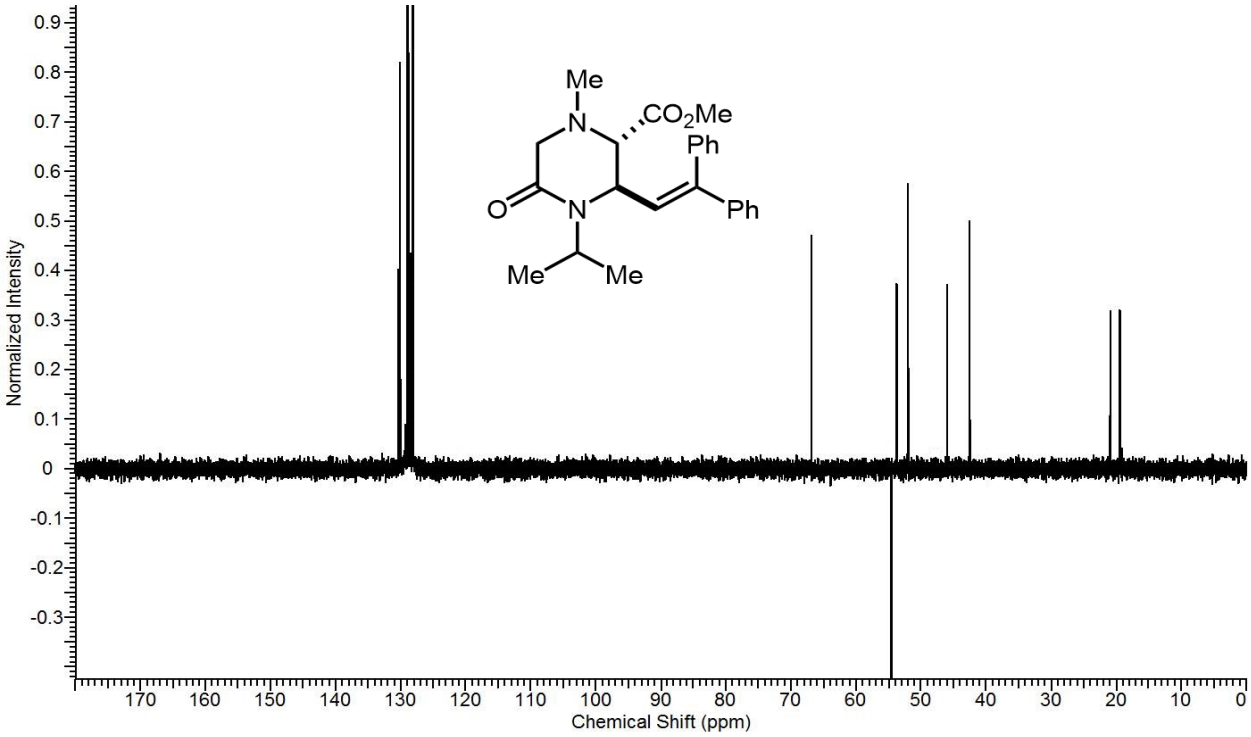
Spectrum 1-**249**: DEPT-135 NMR spectrum of **8d2.**



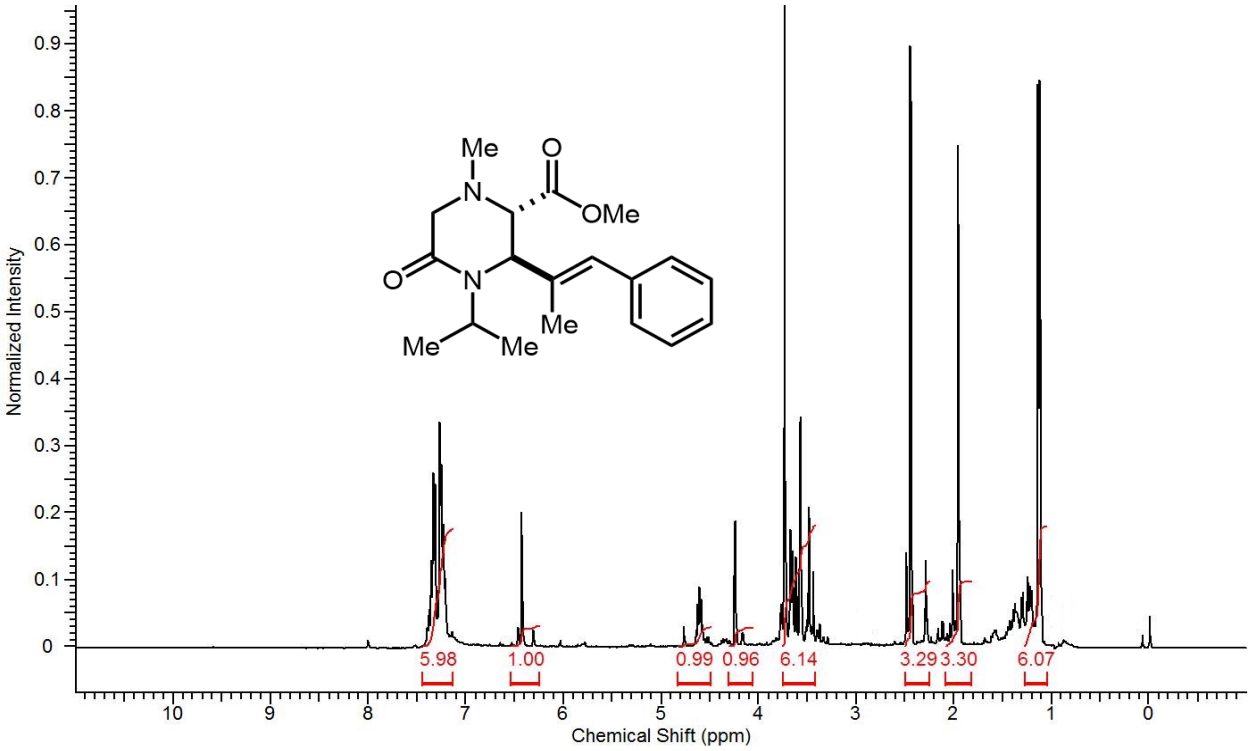
Spectrum 1-**250**: ^{1}H NMR spectrum of **8e2.**



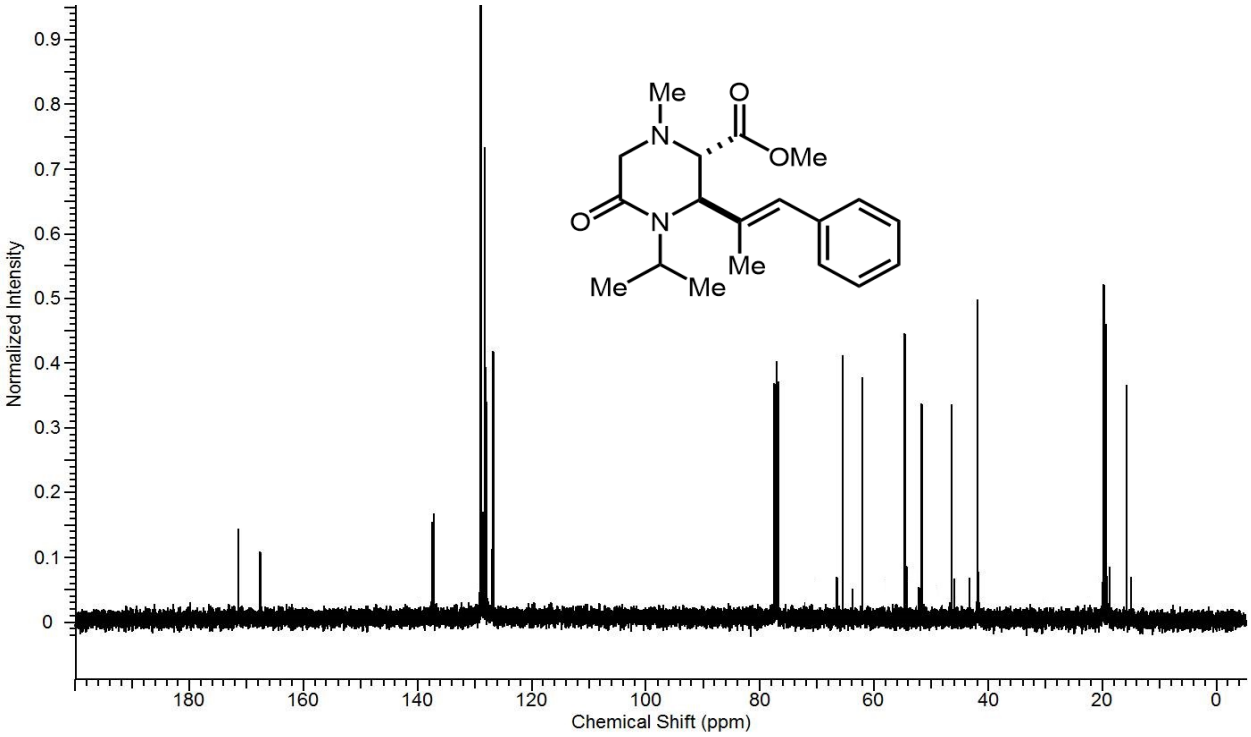
Spectrum 1-**251**: ^{13}C NMR spectrum of **8e2.**



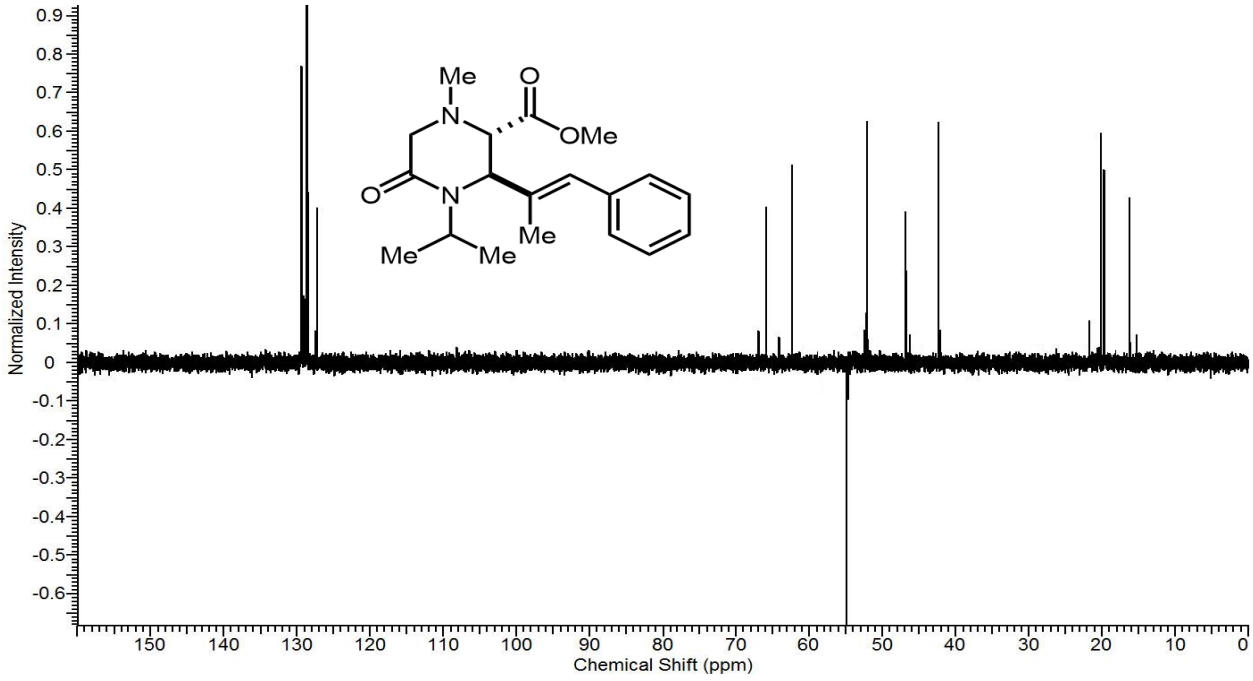
Spectrum 1-**252**: DEPT-135 NMR spectrum of **8e2.**



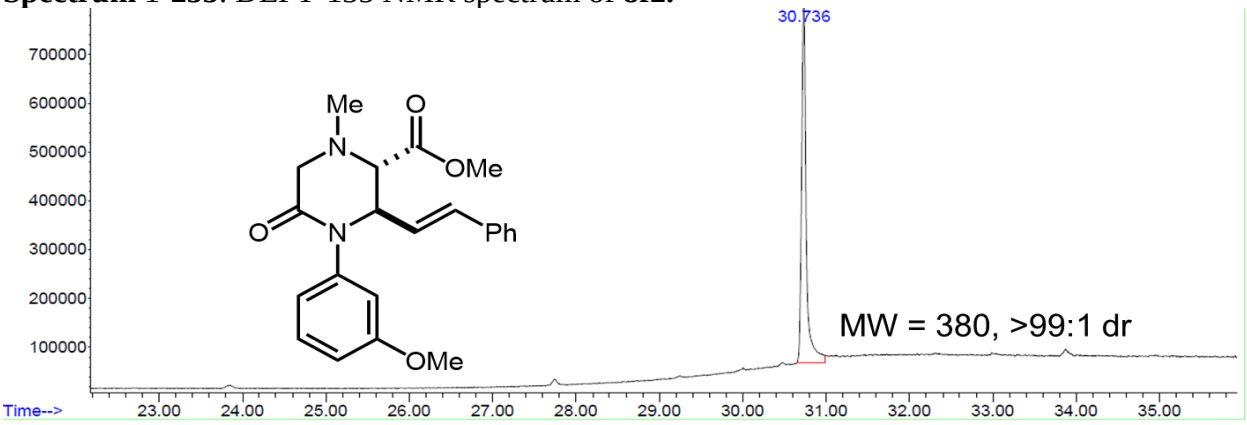
Spectrum 1-**253**: ^{1}H NMR spectrum of **8f2.**

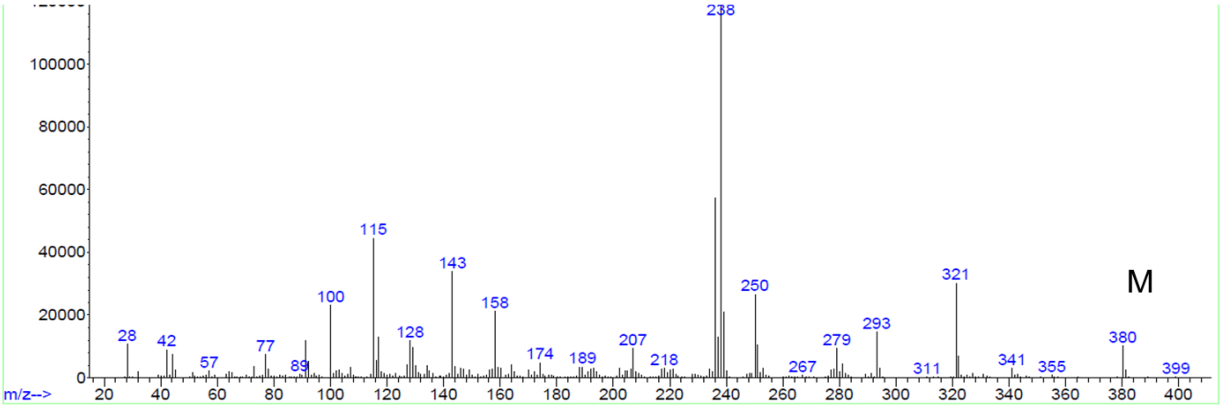


Spectrum 1-**254**: ^{13}C NMR spectrum of **8f2.**

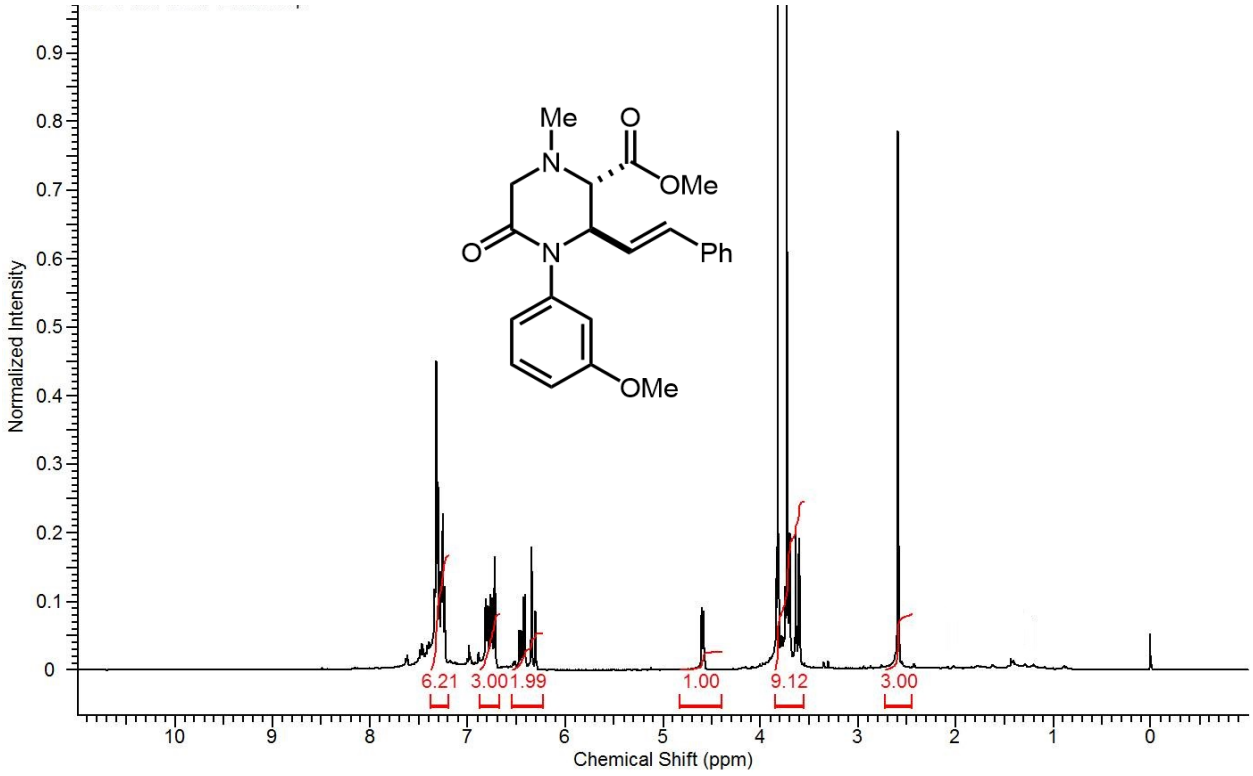


Spectrum 1-**255**: DEPT-135 NMR spectrum of **8f2.**

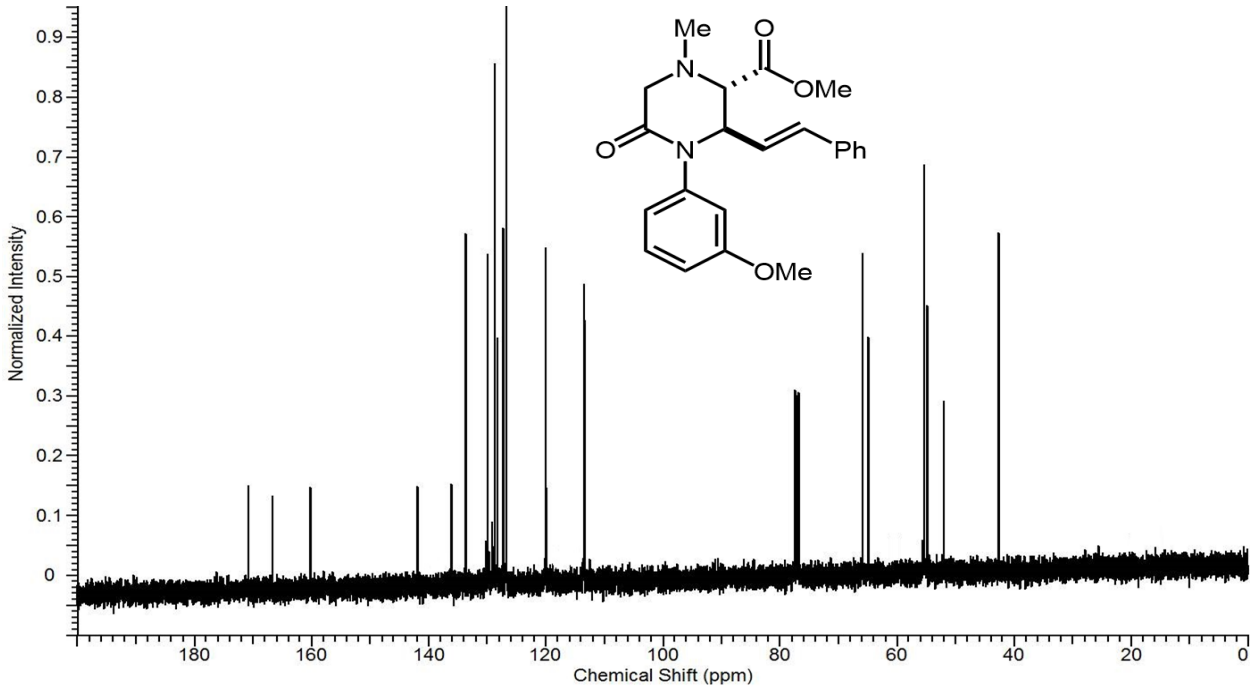




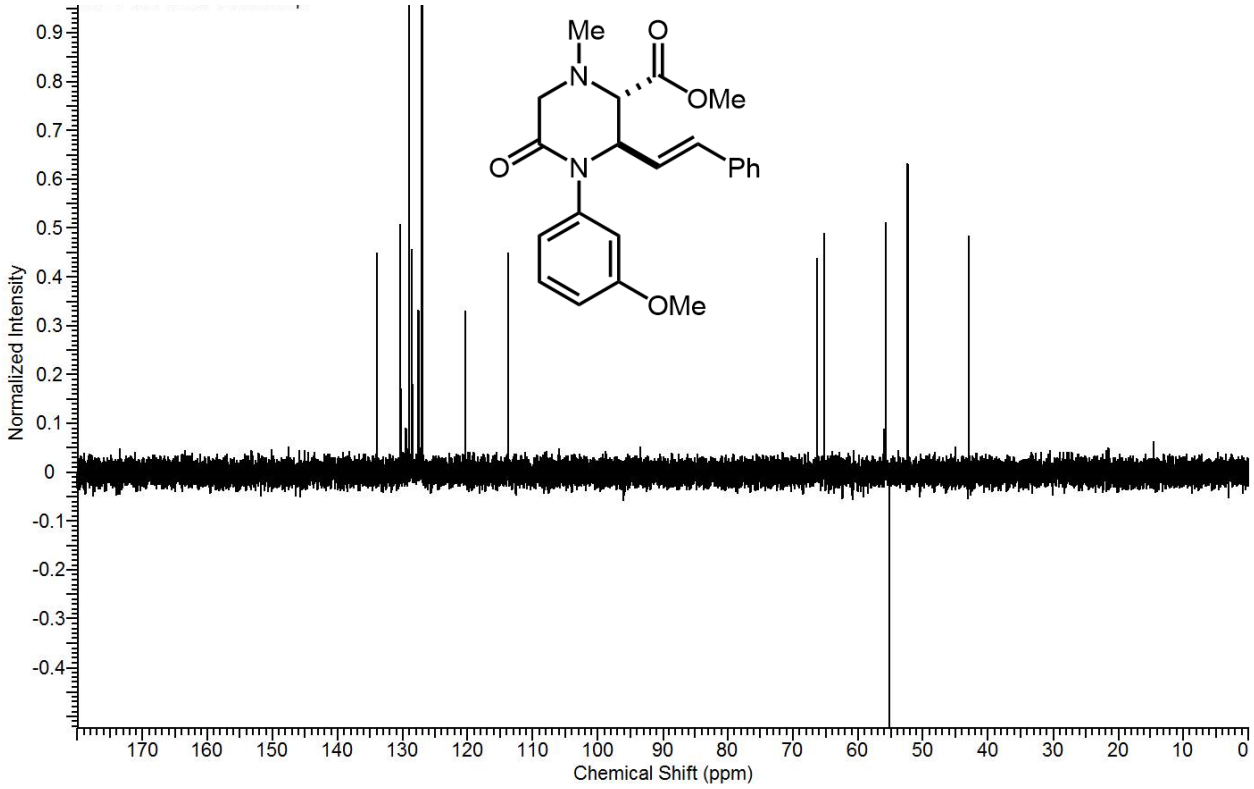
Spectrum 1-**256 and 1-257**: GC and MS spectra of **8g2.**



Spectrum 1-**258**: ^{1}H NMR spectrum of **8g2.**

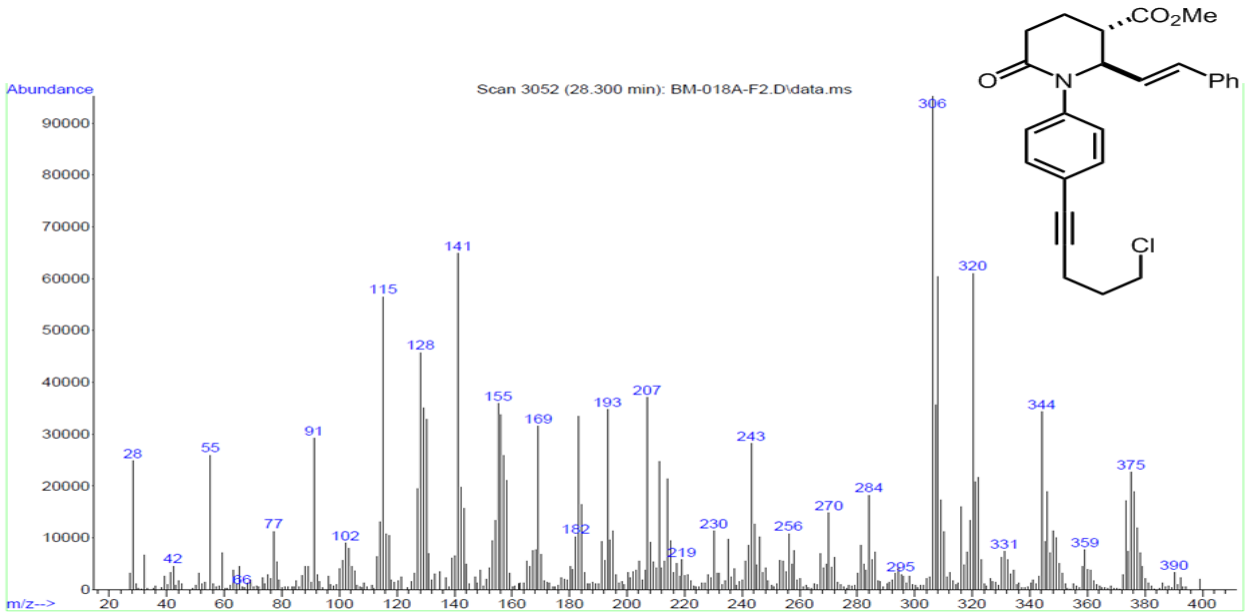


Spectrum 1-**259**: ^{13}C NMR spectrum of **8g2.**

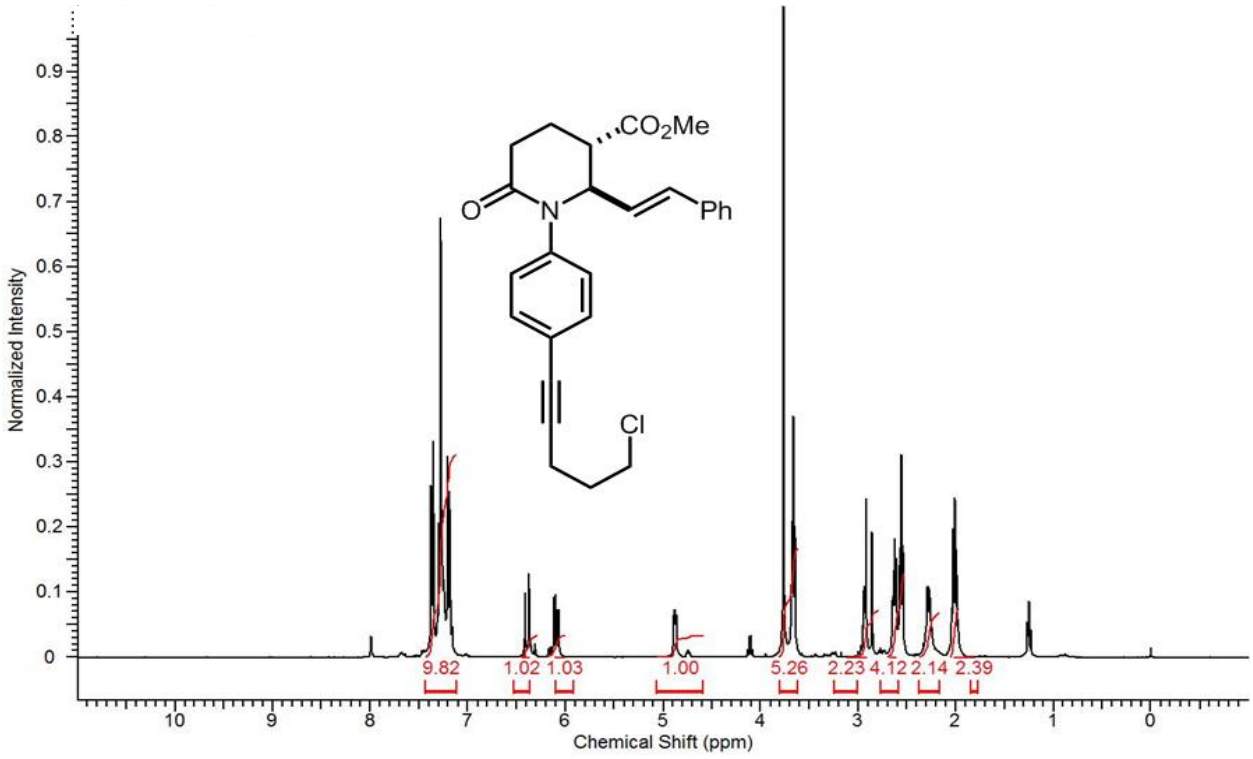


Spectrum 1-**260**: DEPT-135 NMR spectrum of **8g2.**

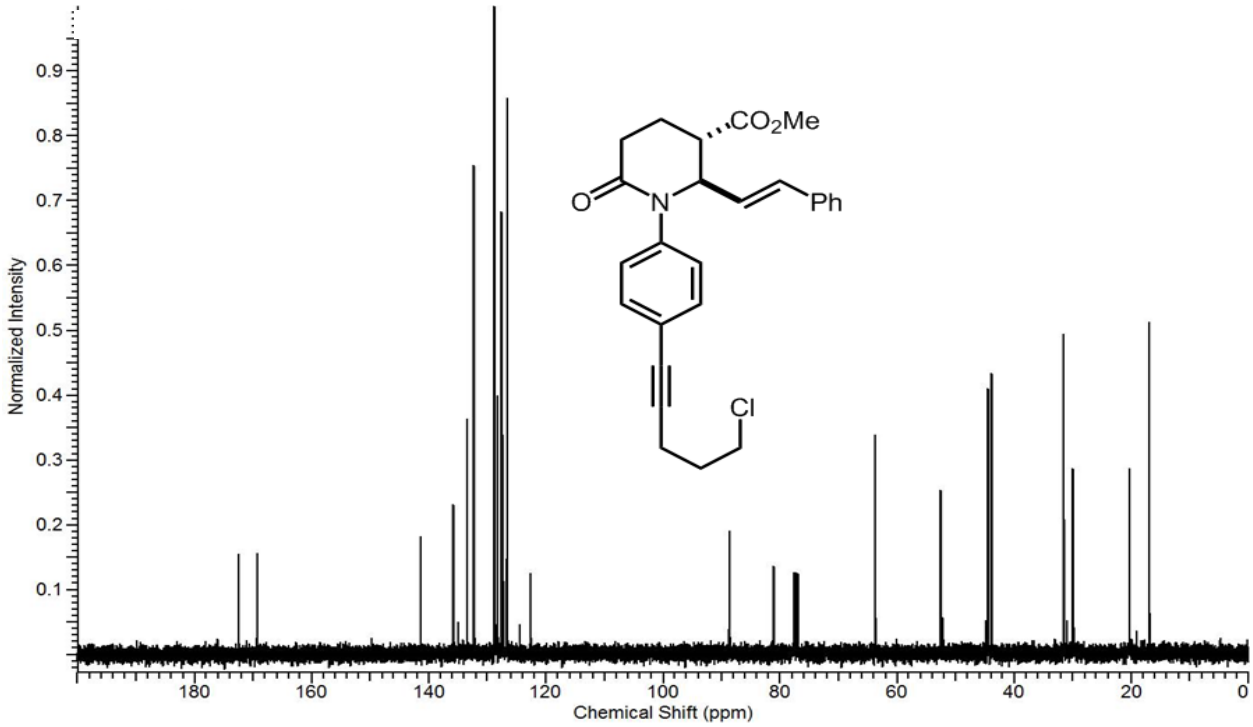
Appendix B: Spectral Data for Chapter 3



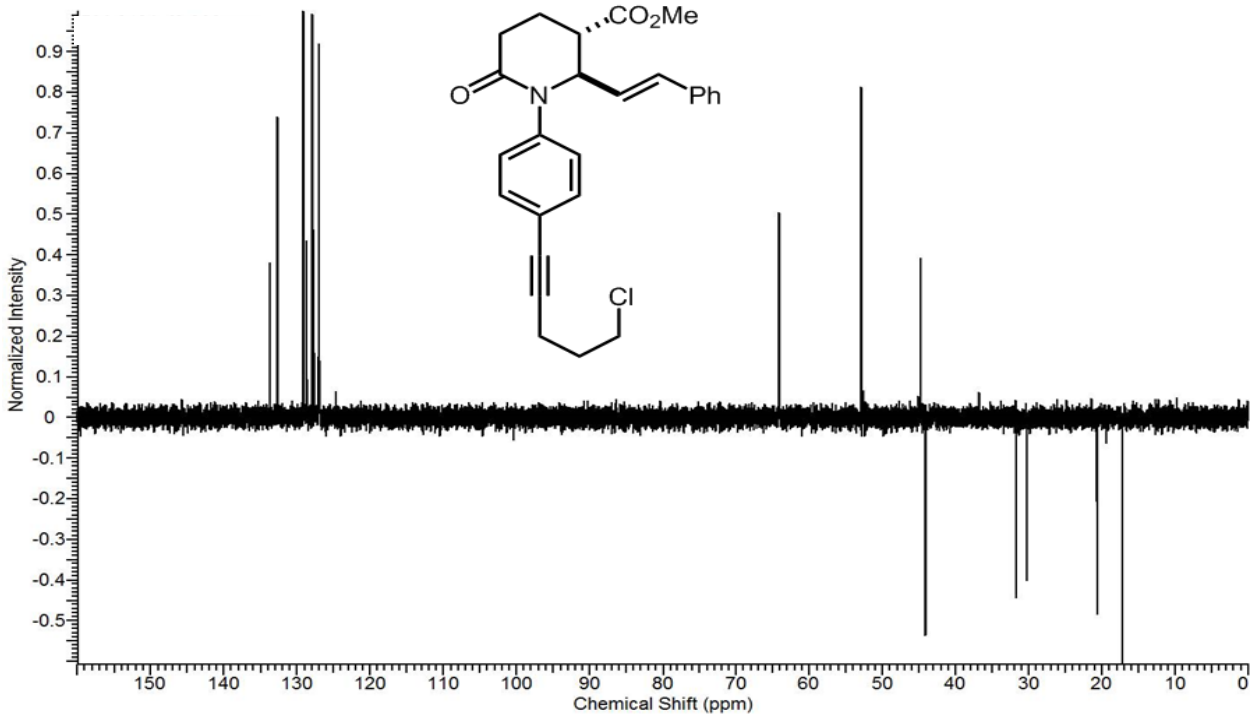
Spectrum 2-1: GC spectrum of **10a1.**



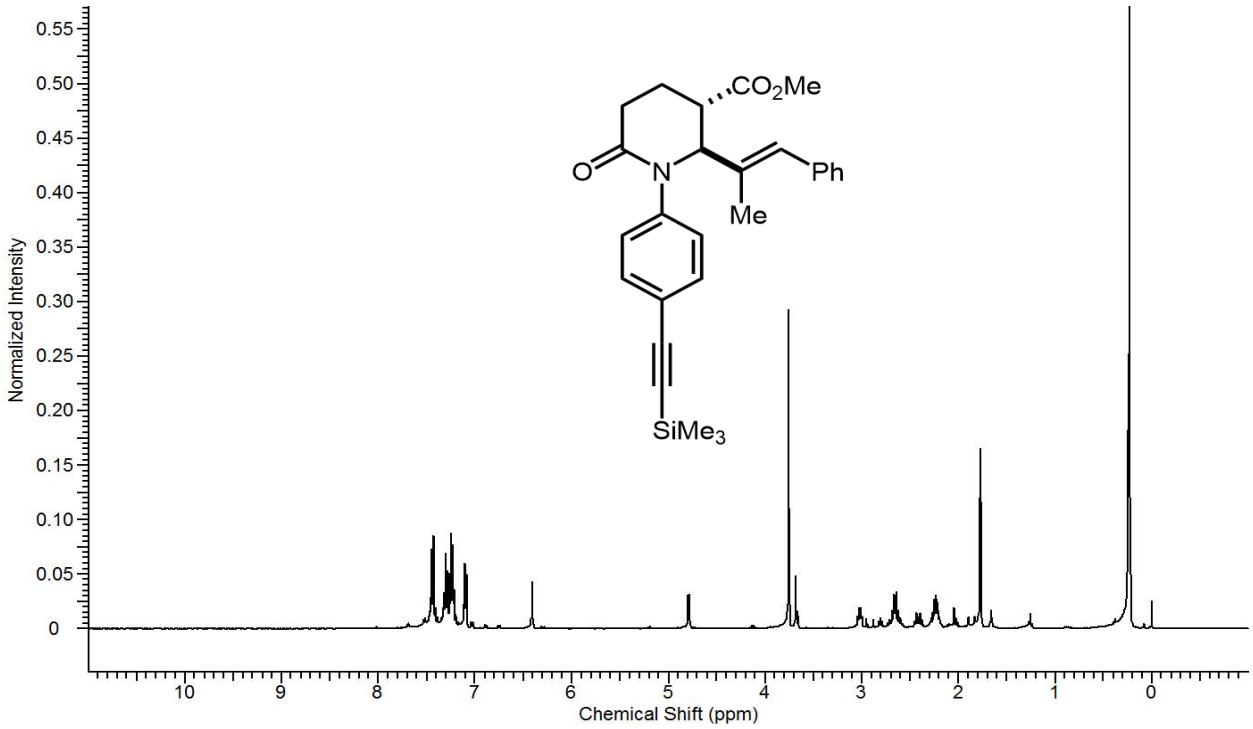
Spectrum 2-2: ^{1}H NMR spectrum of **10a1.**



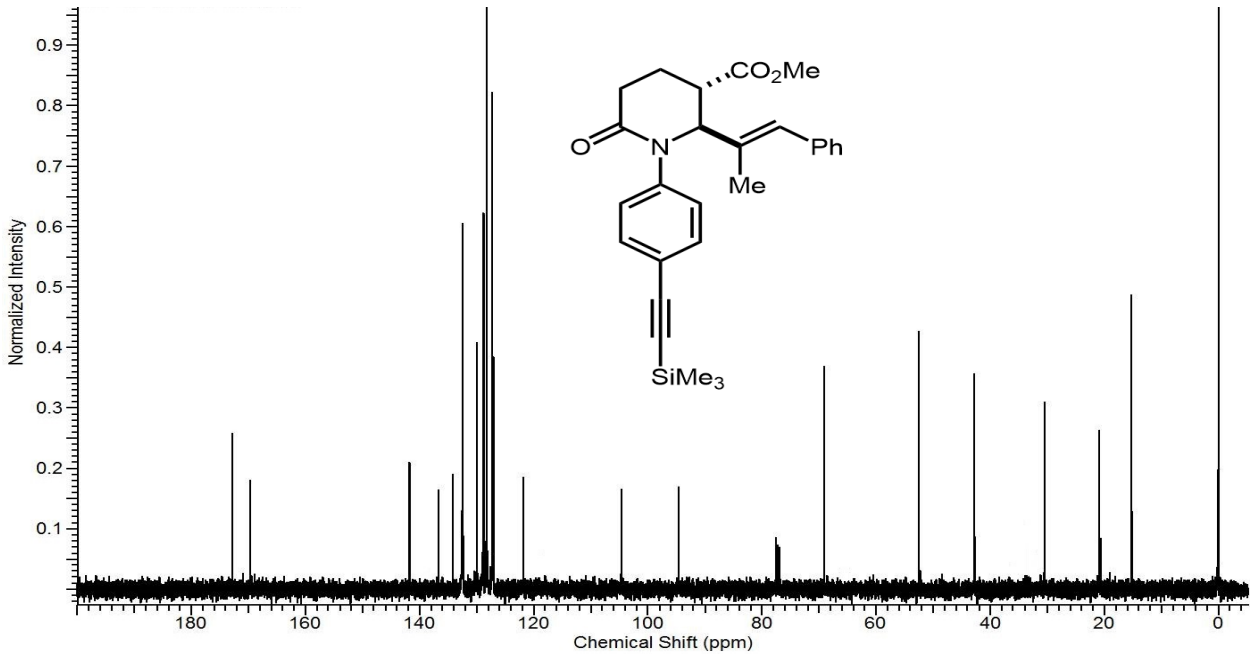
Spectrum 2-3: ^{13}C NMR spectrum of **10a1.**



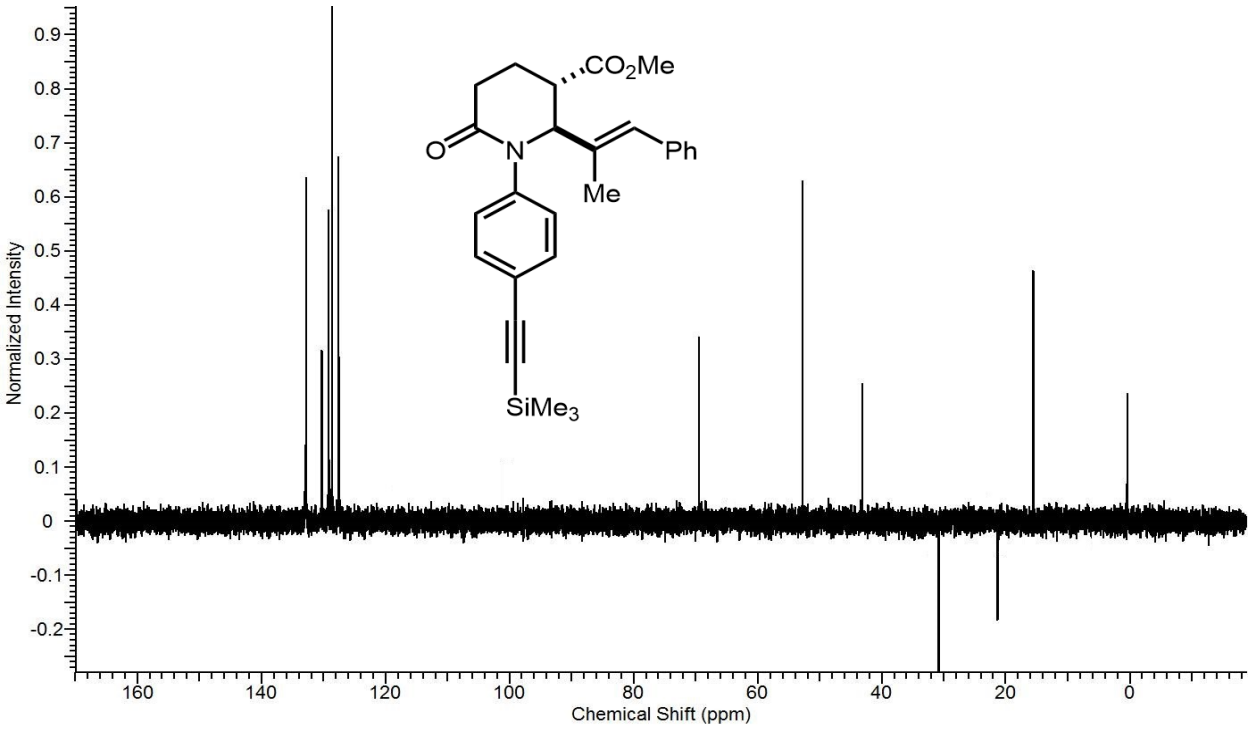
Spectrum 2-4: DEPT-135 NMR spectrum of **10a1.**



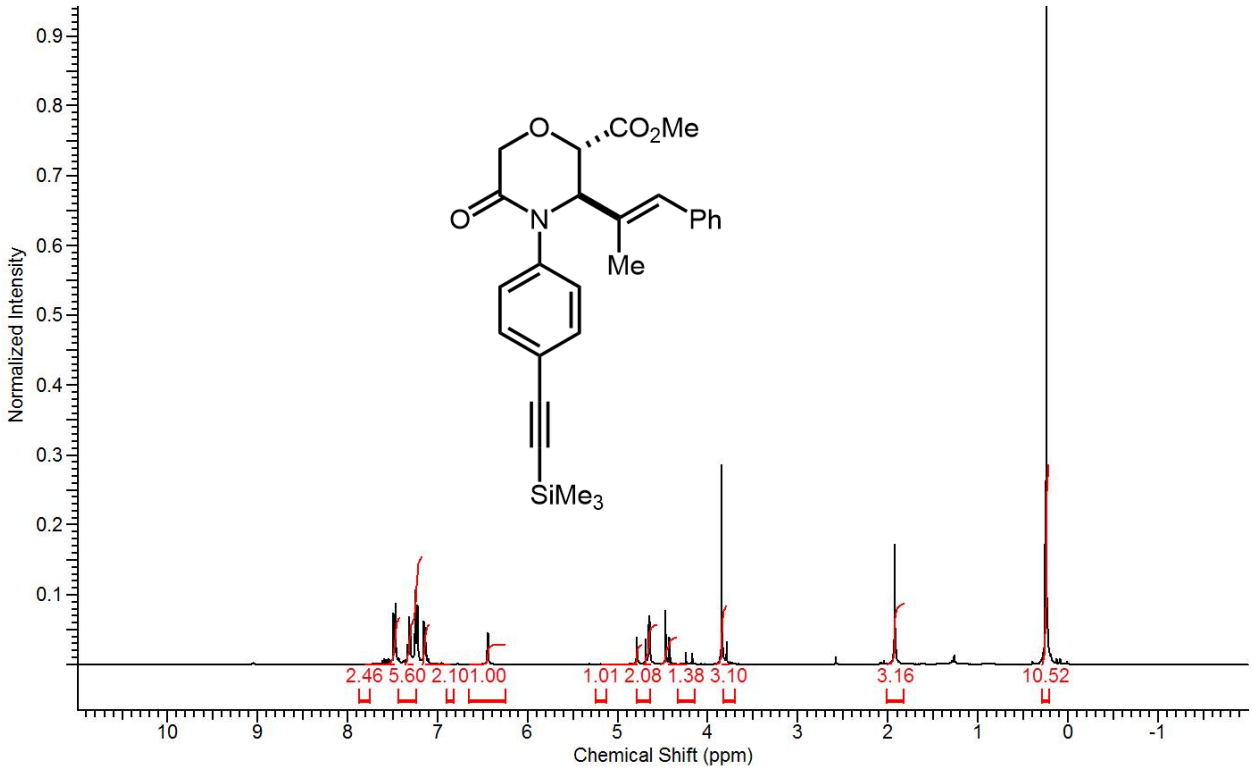
Spectrum 2-5: ^{1}H NMR spectrum of **10a2.**



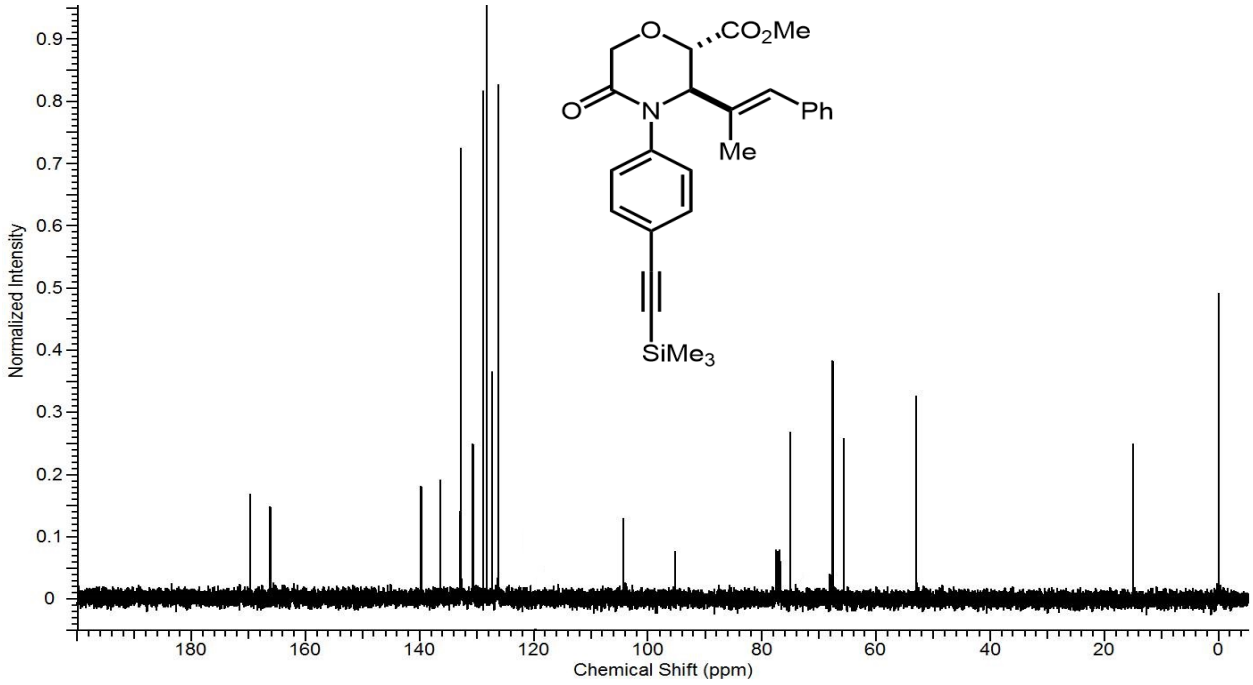
Spectrum 2-6: ^{13}C NMR spectrum of **10a2.**



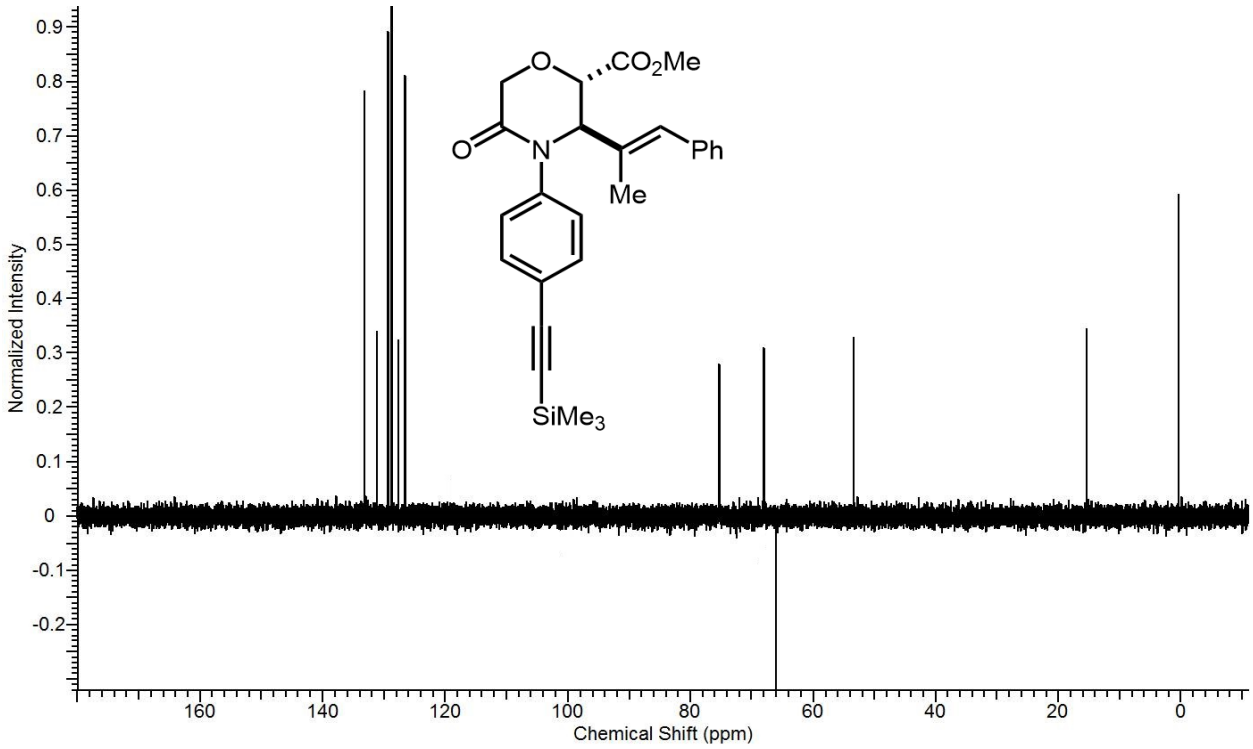
Spectrum 2-7: DEPT135 NMR spectrum of **10a2.**



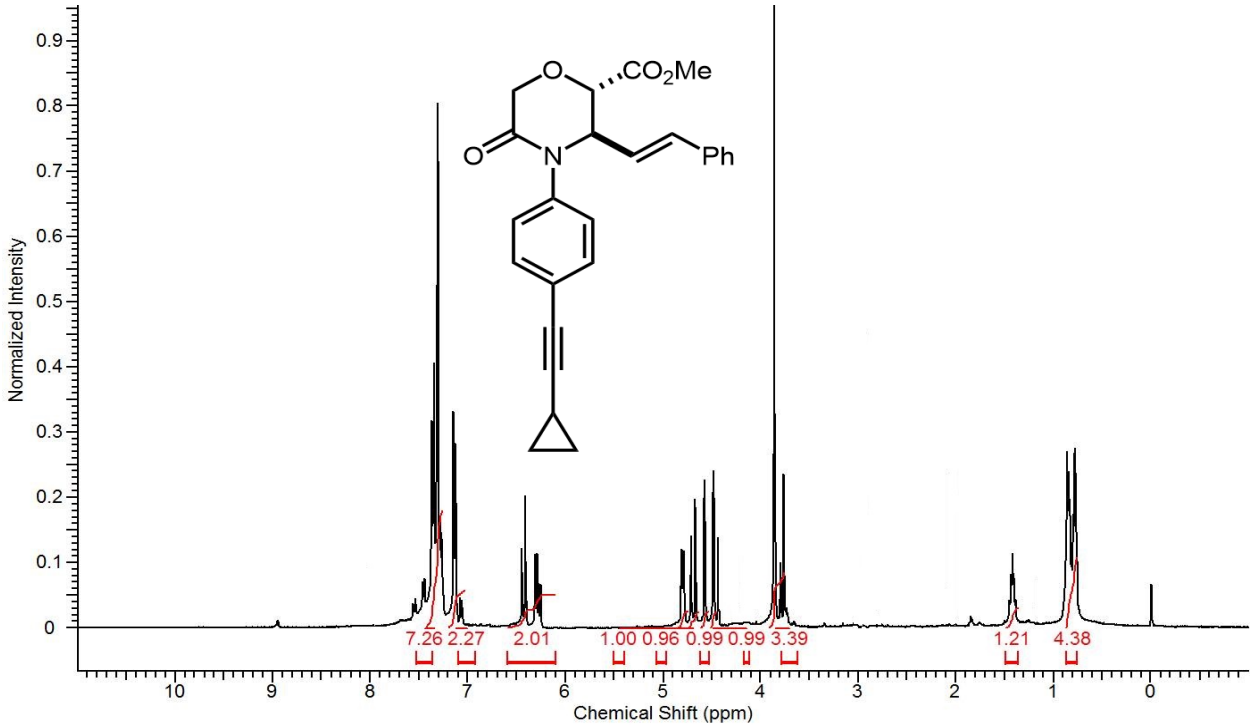
Spectrum 2-8: ^{1}H NMR spectrum of **10a3.**



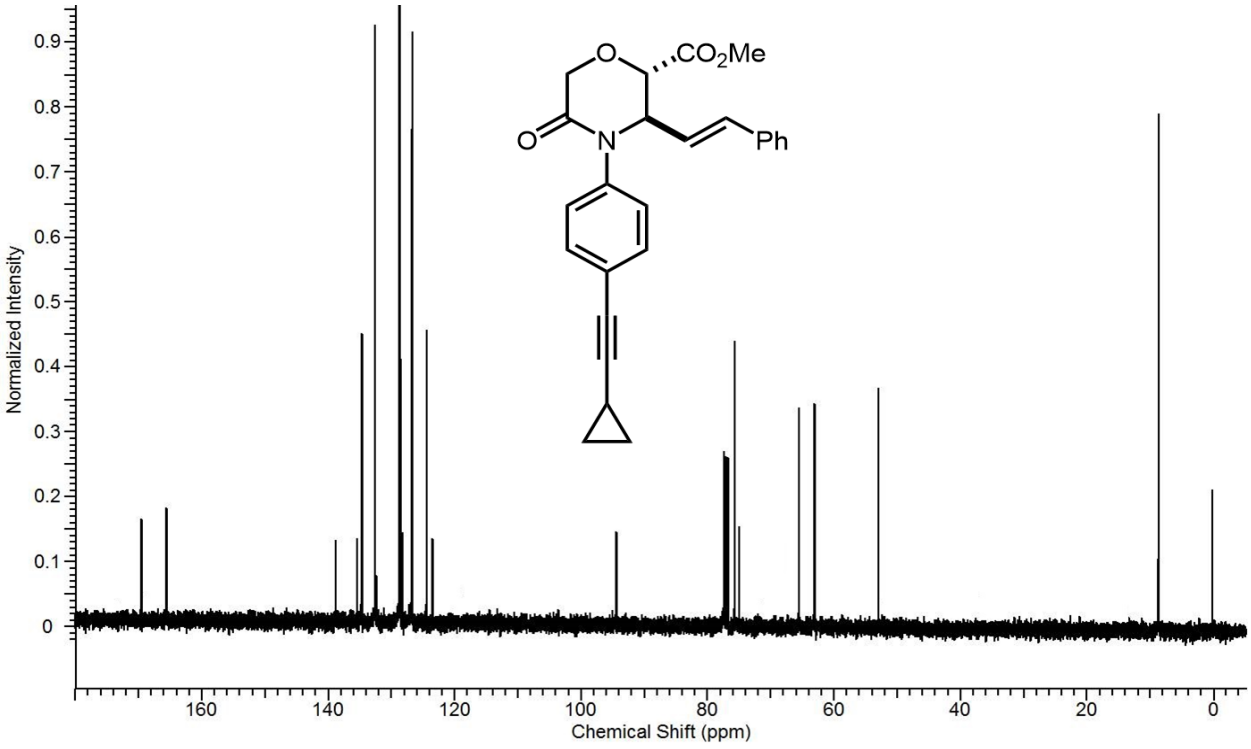
Spectrum 2-9: ^{13}C NMR spectrum of **10a3.**



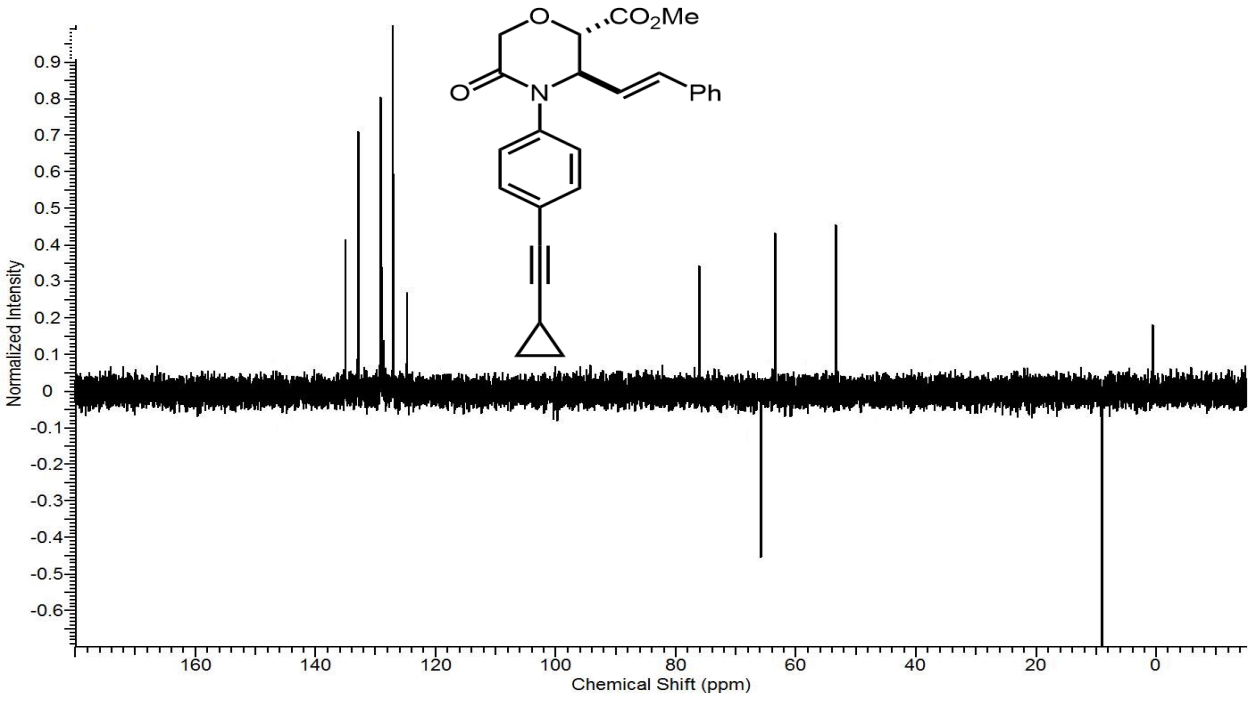
Spectrum 2-10: DEPT-135 NMR spectrum of **10a3.**



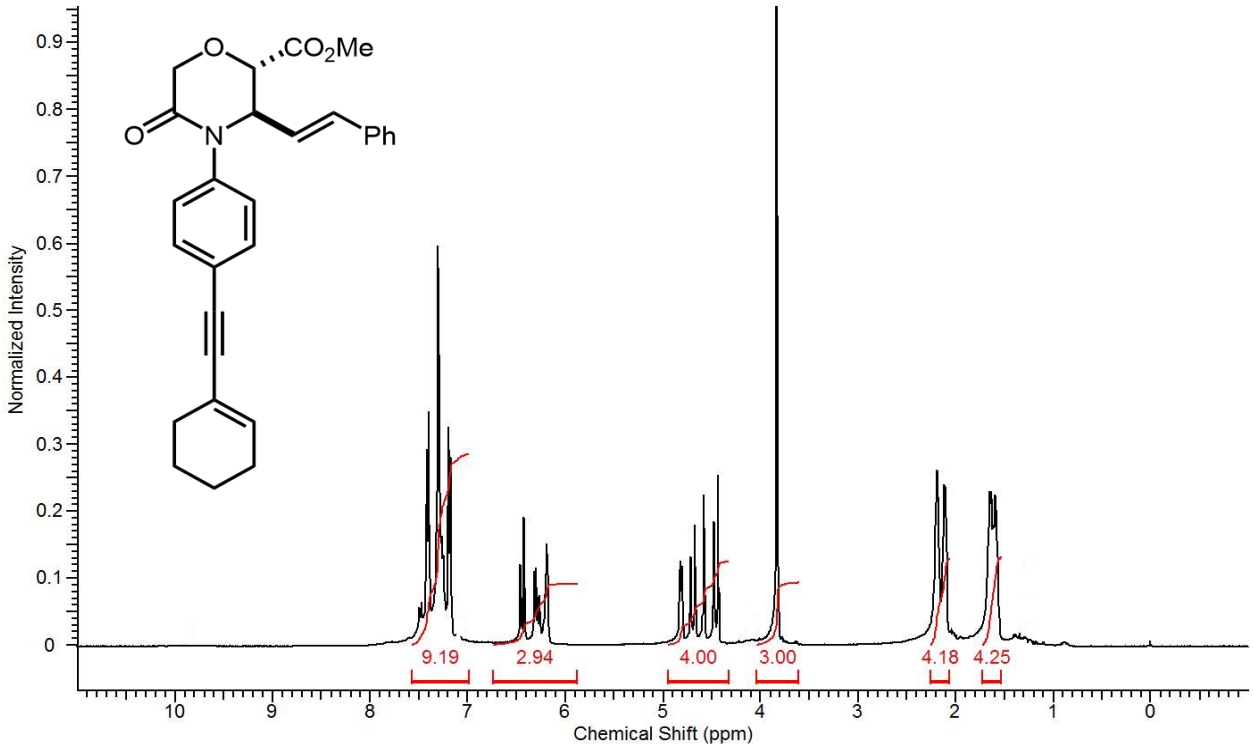
Spectrum 2-11: ^{1}H NMR spectrum of **10a4.**



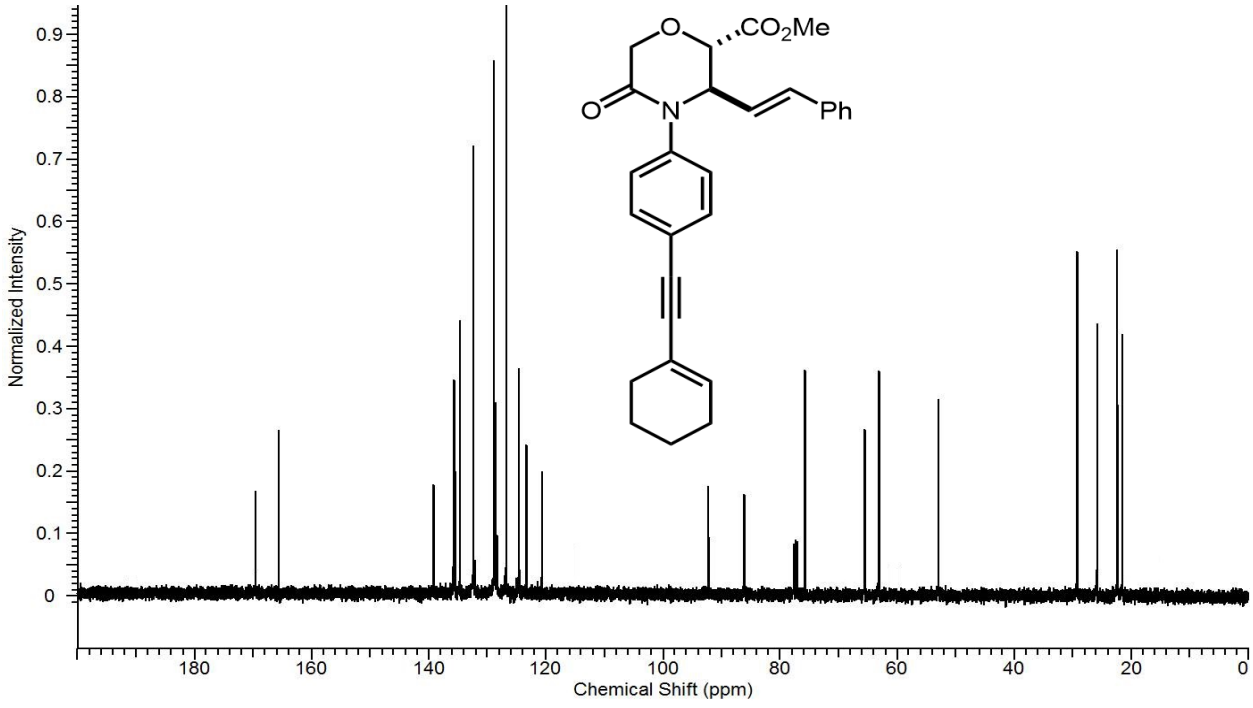
Spectrum 2-12: ^{13}C NMR spectrum of **10a4.**



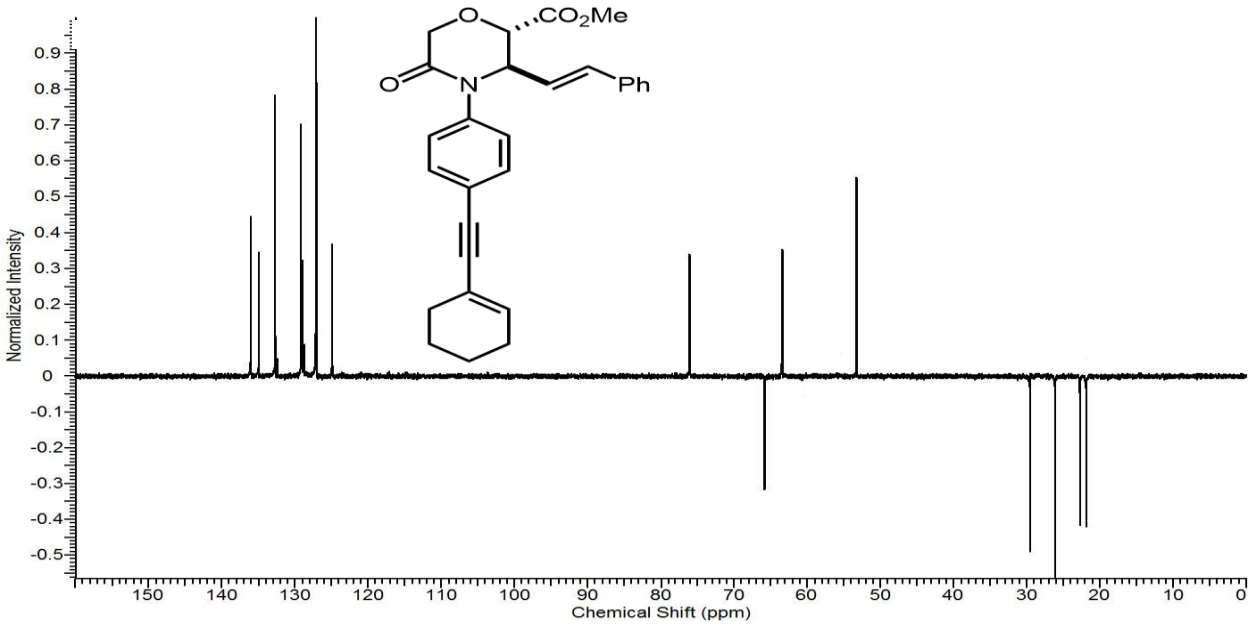
Spectrum 2-13: DEPT-135 NMR spectrum of **10a4.**



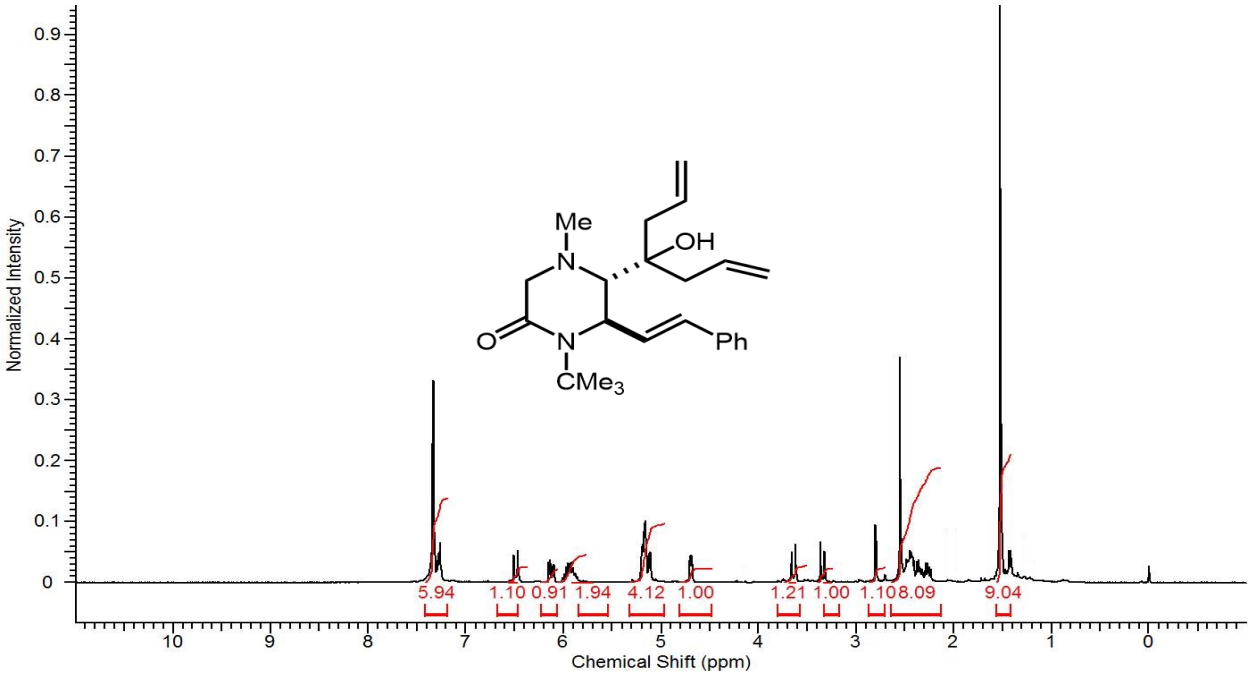
Spectrum 2-14: ^{1}H NMR spectrum of **10a5.**



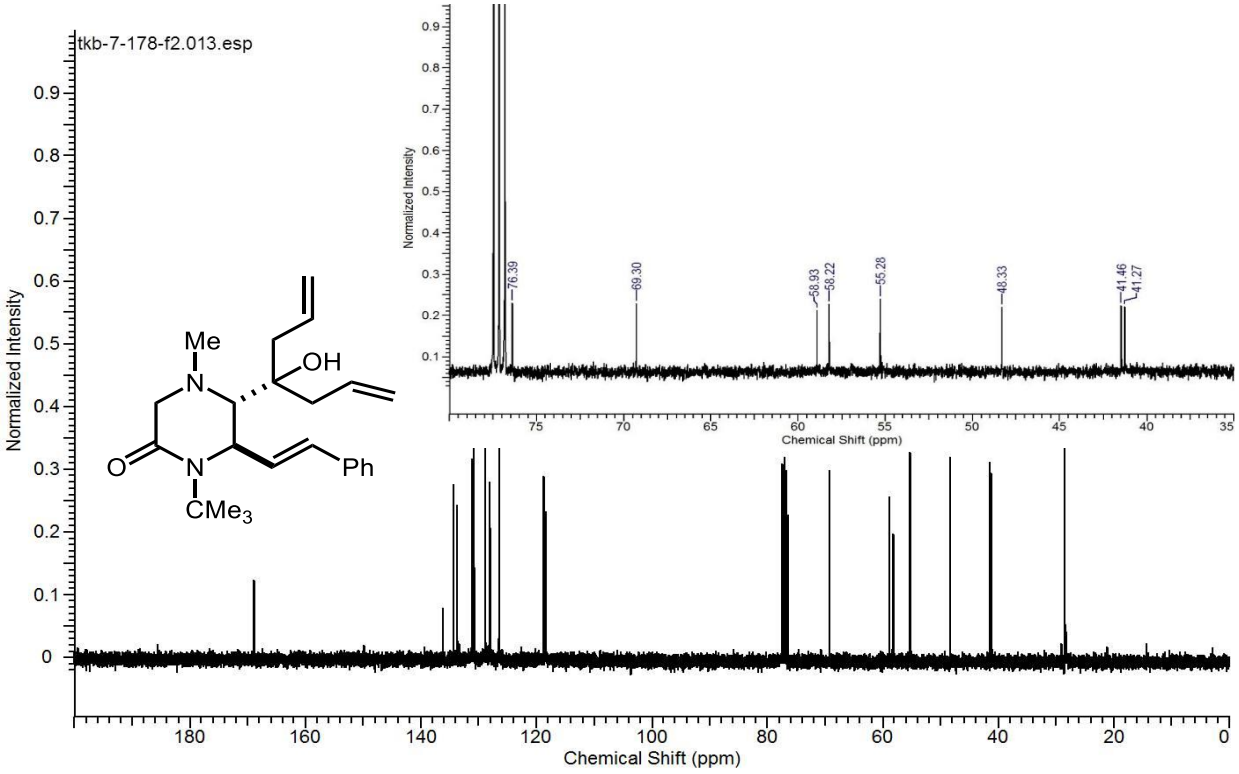
Spectrum 2-15: ^{13}C NMR spectrum of **10a5.**



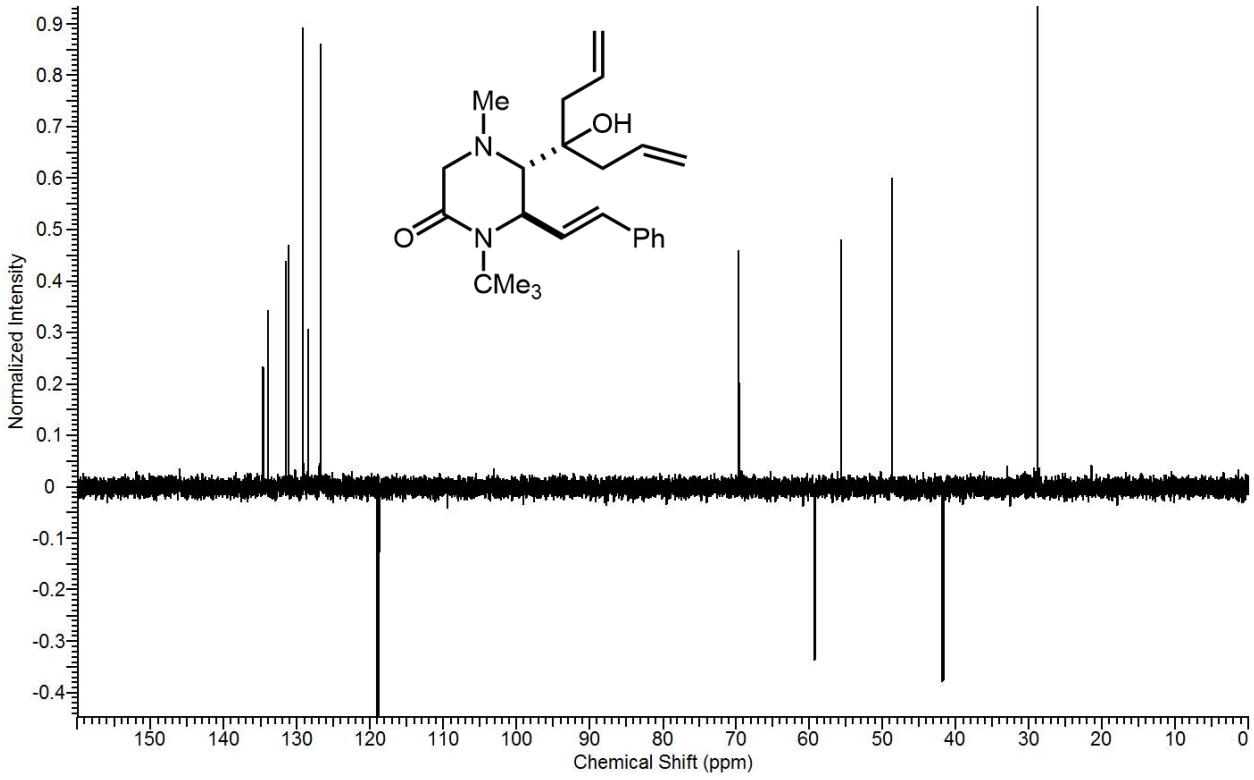
Spectrum 2-16: DEPT-135 NMR spectrum of **10a5.**



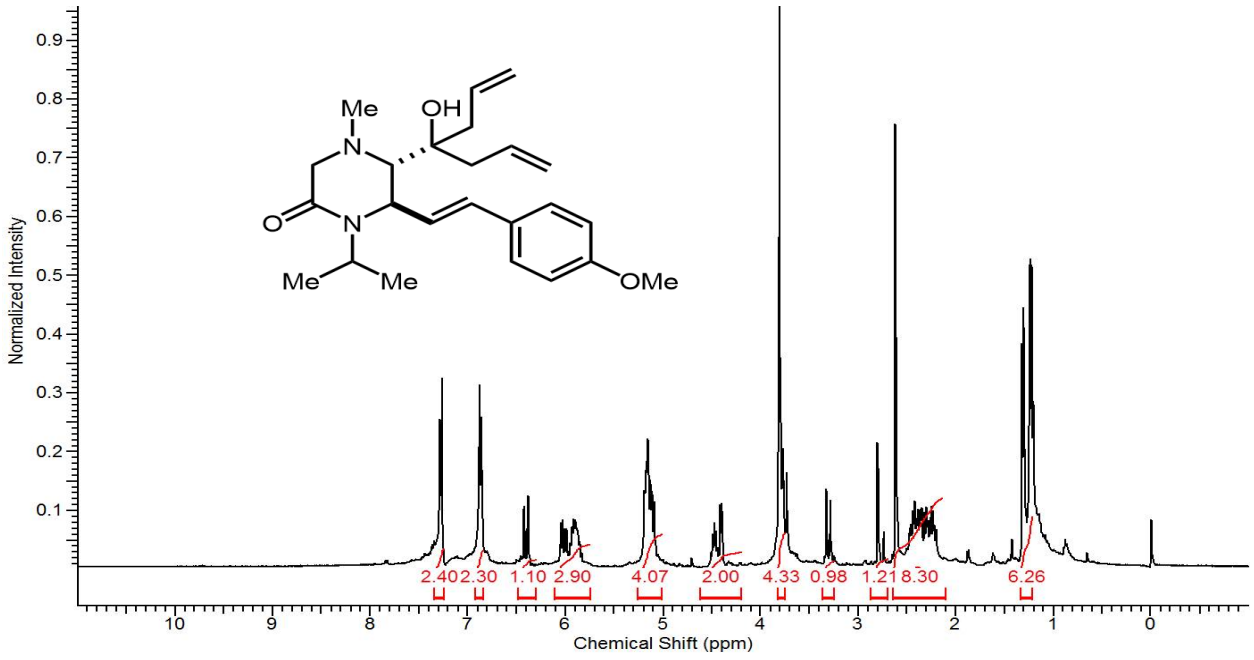
Spectrum 2-17: ^{1}H NMR spectrum of **11a.**



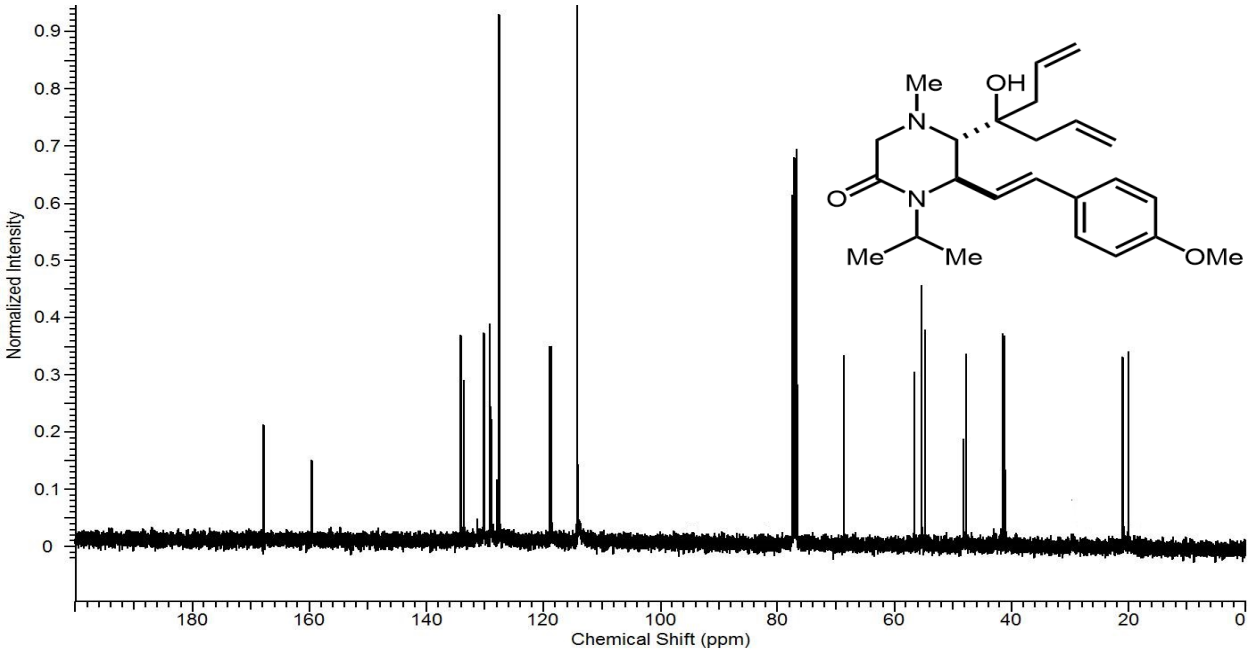
Spectrum 2-18: ^{13}C NMR spectrum of **11a** (zoomed-in spectra included).



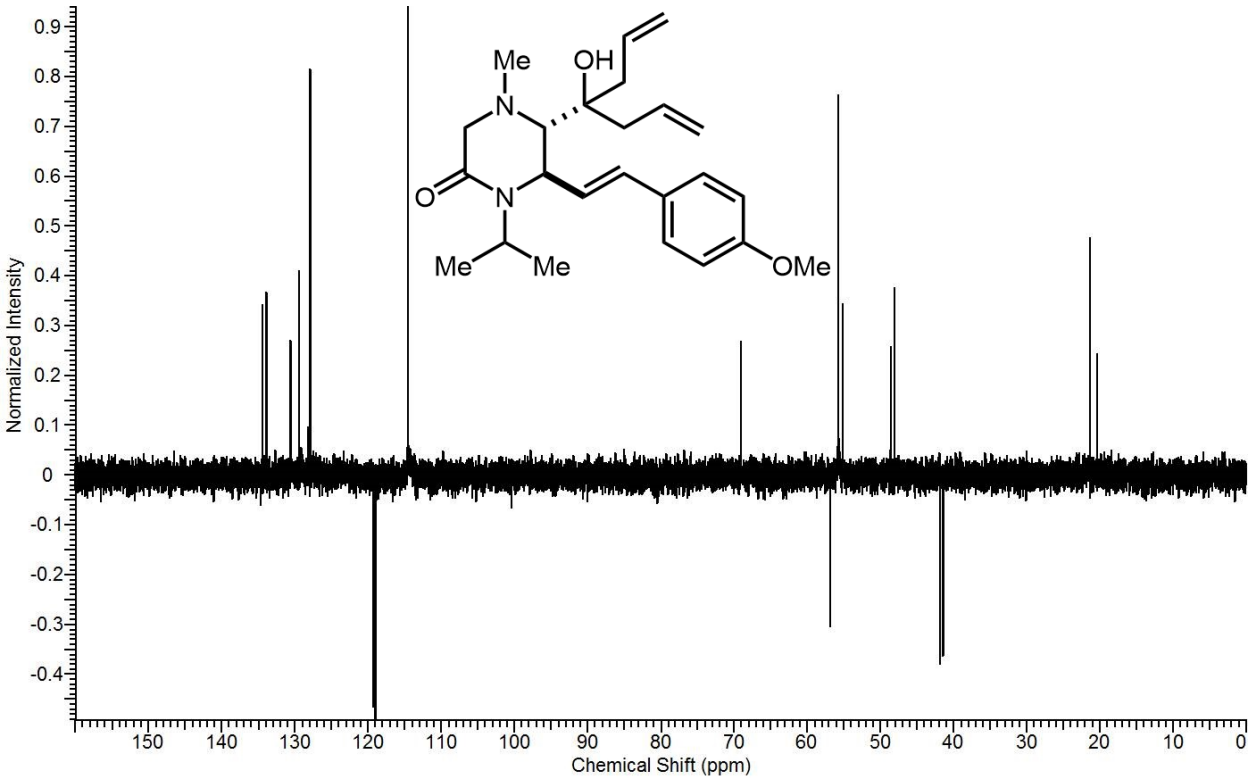
Spectrum 2-19: DEPT-135 NMR spectrum of **11a.**



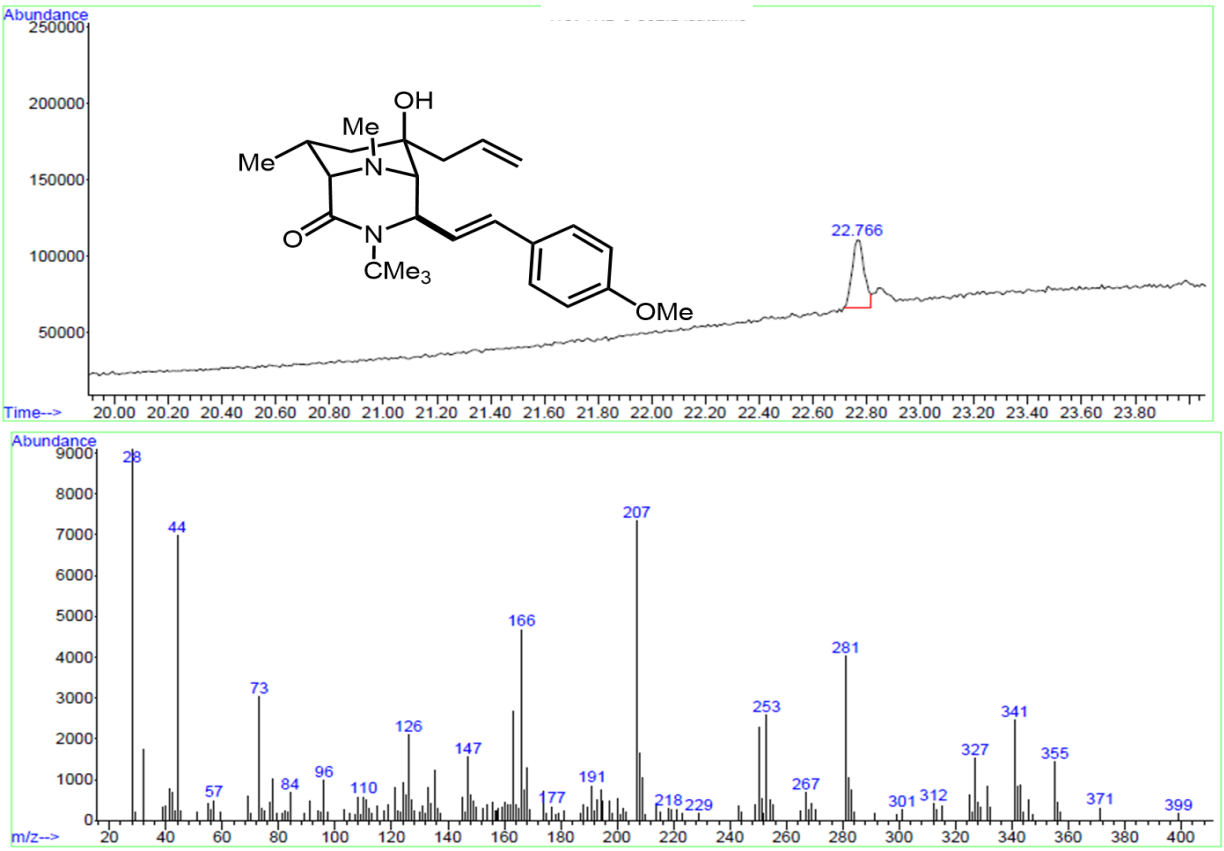
Spectrum 2-20: ^{1}H NMR spectrum of **11b.**



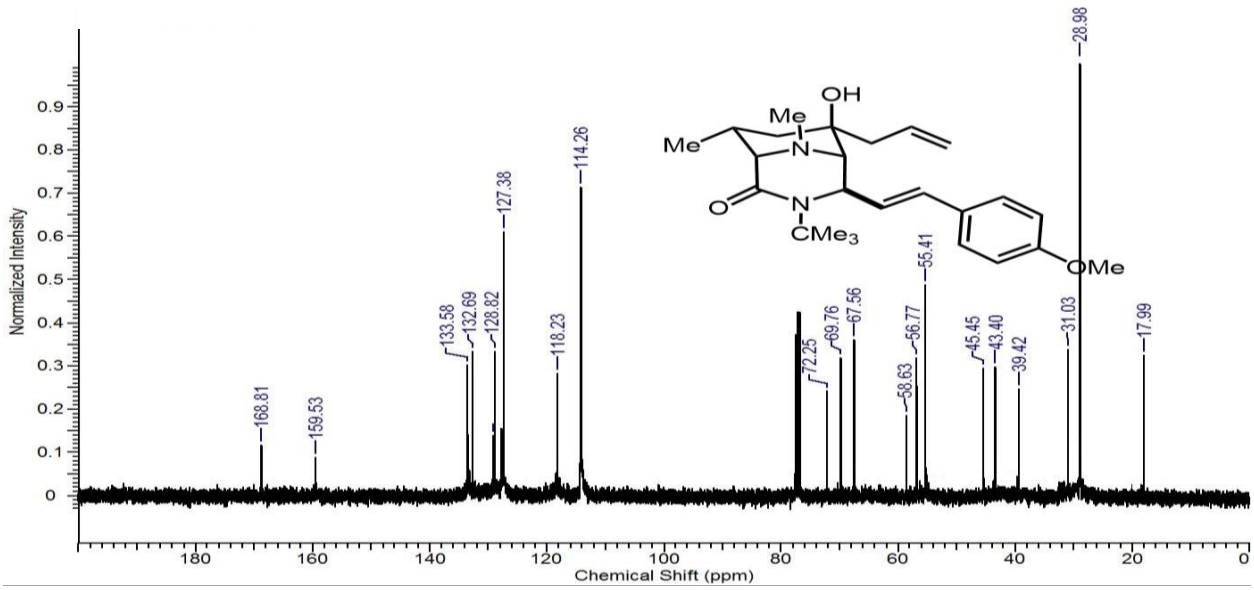
Spectrum 2-21: ^{13}C NMR spectrum of **11b.**



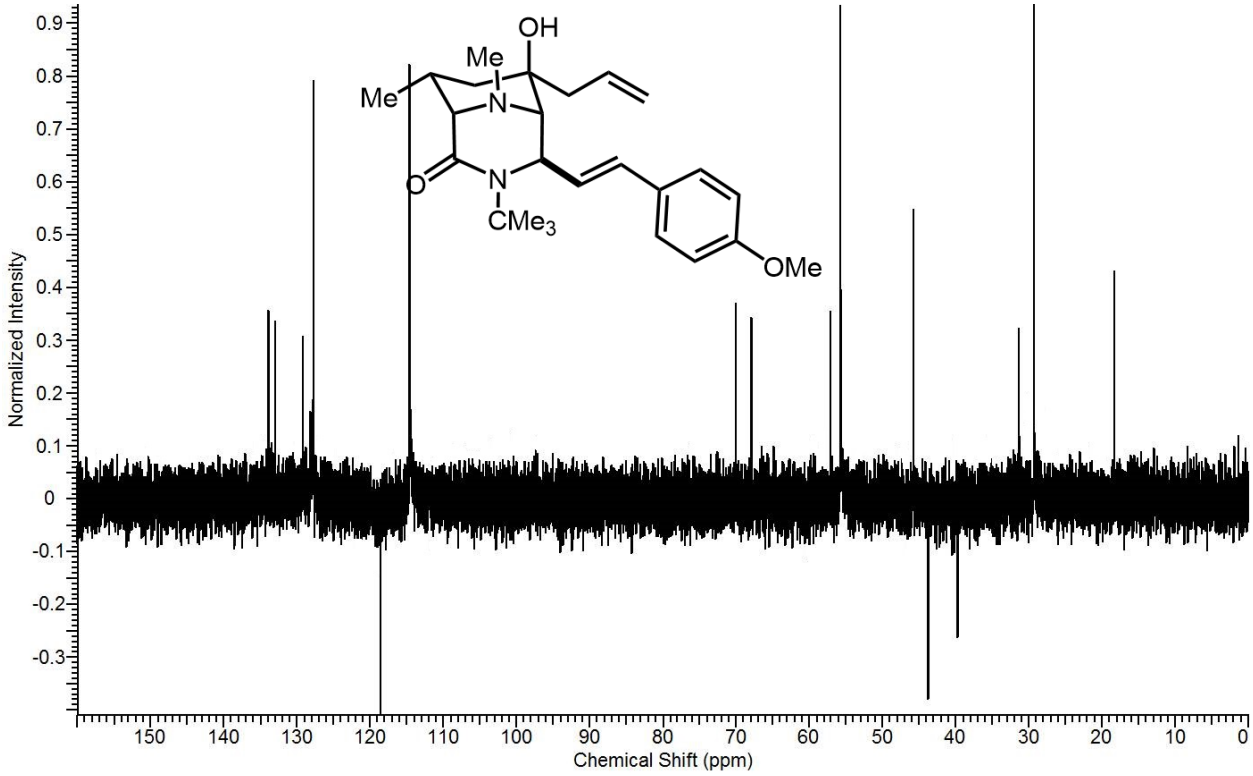
Spectrum 2-22: DEPT-135 NMR spectrum of **11b.**



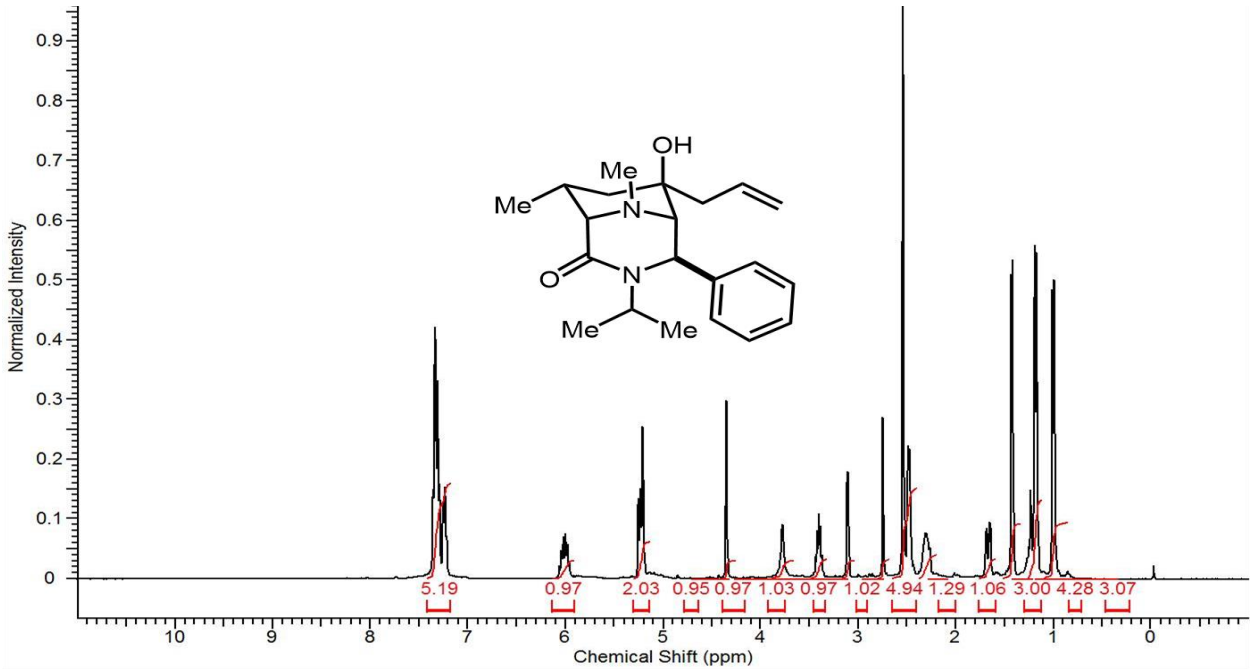
Spectrum 2-23 and 2-24: GC and MS spectra of **12** (extracted from mixture with **11c**).



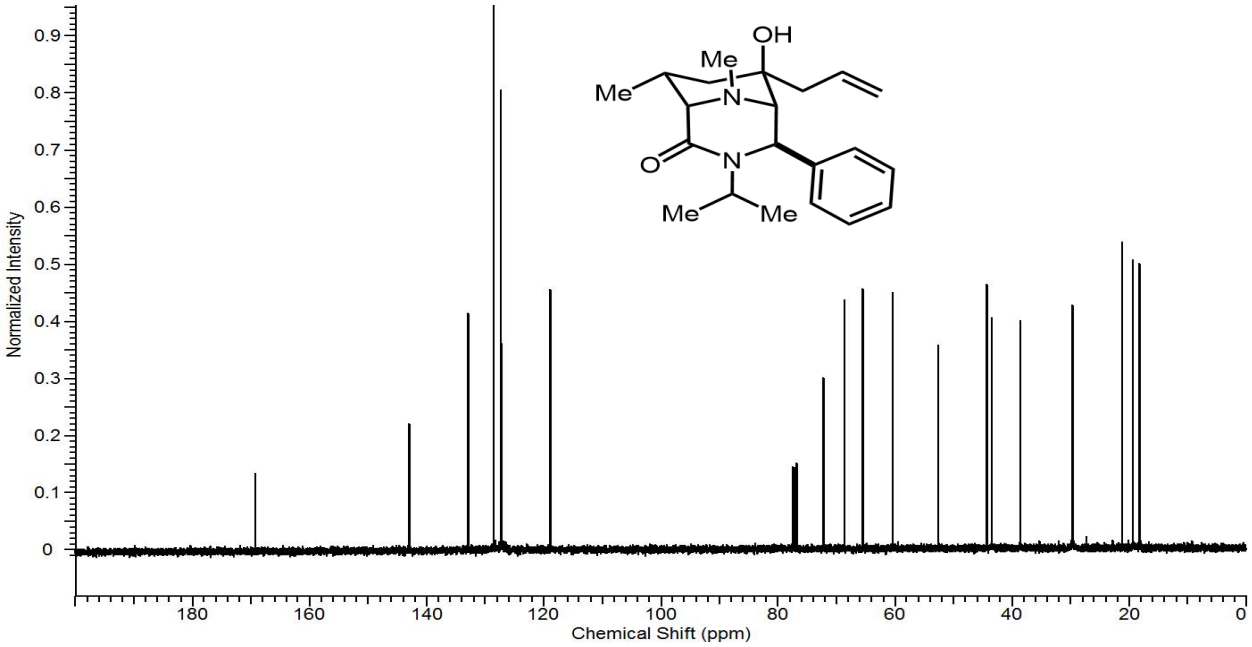
Spectrum 2-25: ^{13}C NMR spectrum of **12** (extracted from mixture with **11c**).



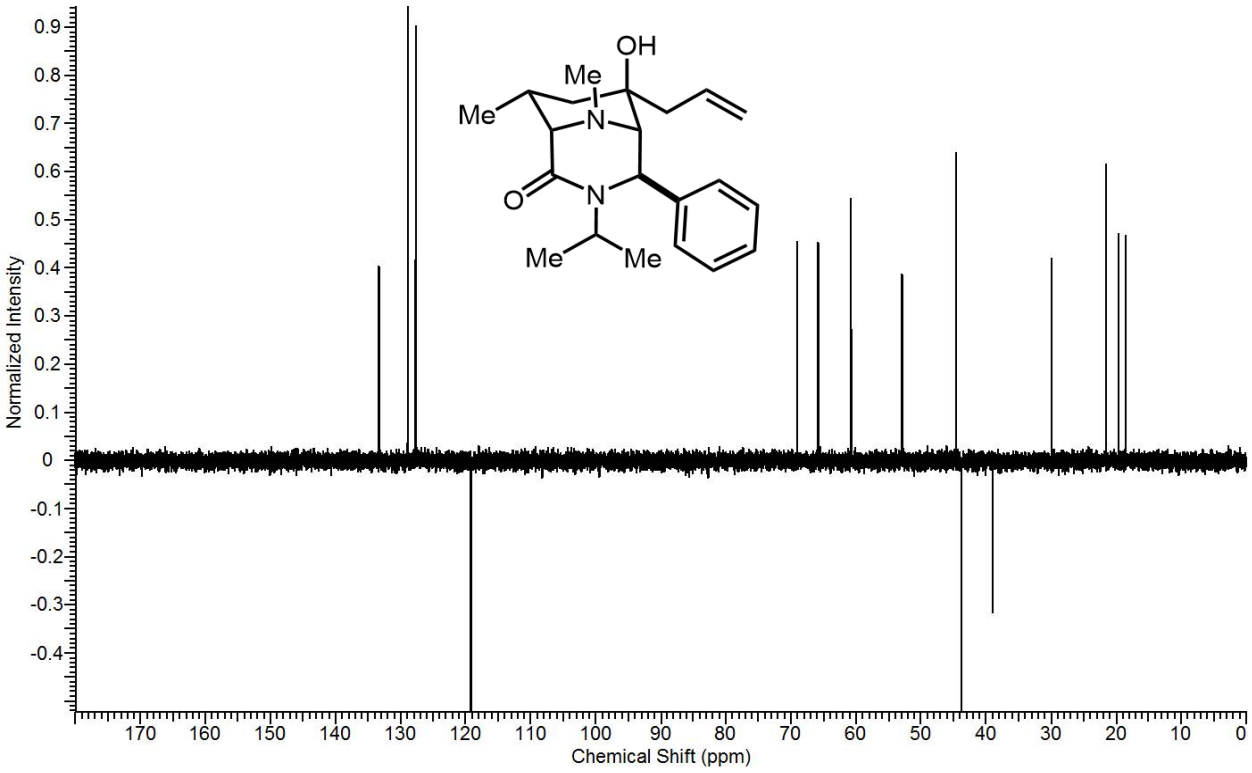
Spectrum 2-26: DEPT-135 NMR spectrum of **12** (extracted from mixture with **11c**).



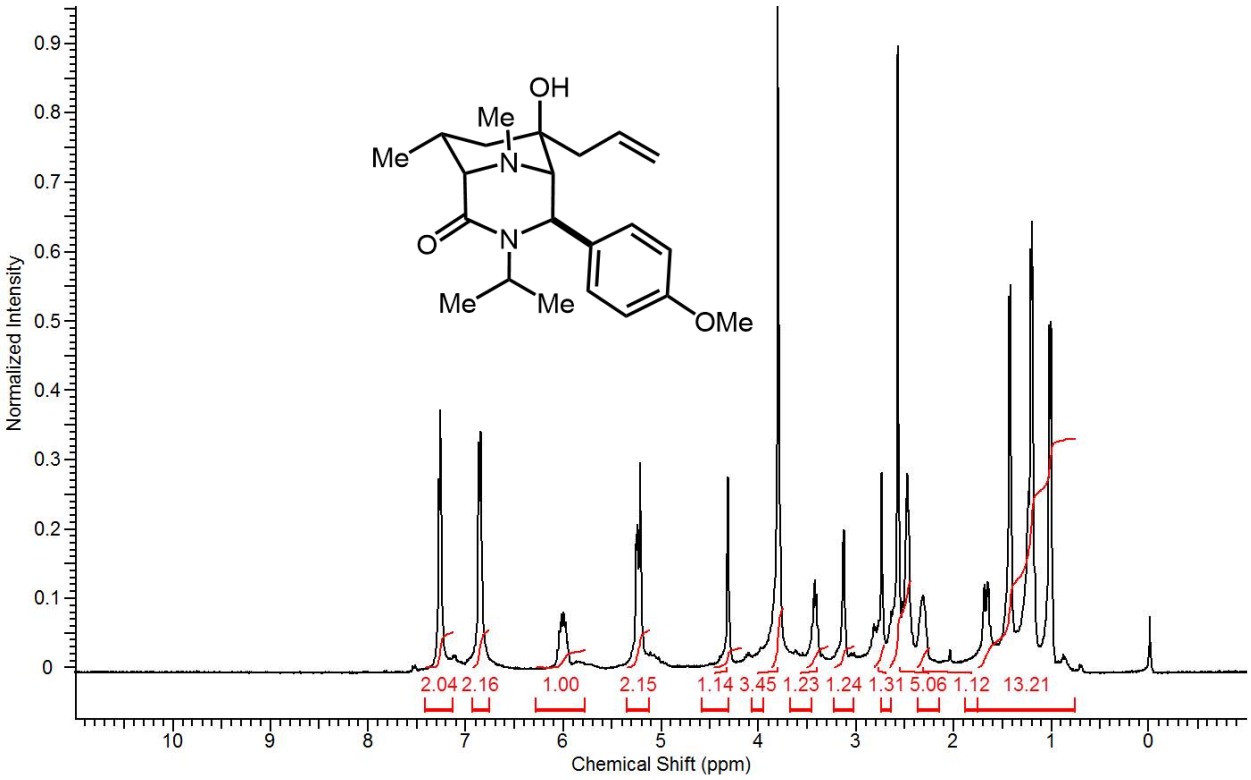
Spectrum 2-27: ^{1}H NMR spectrum of **13a.**



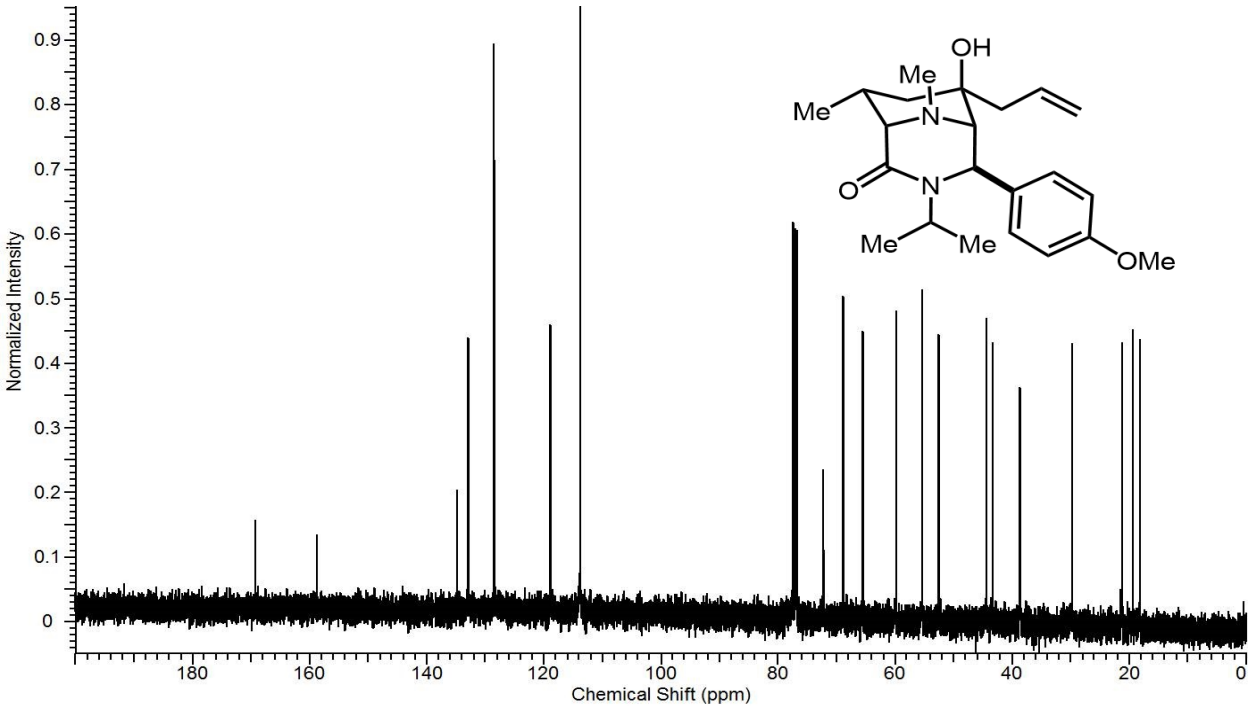
Spectrum 2-28: ^{13}C NMR spectrum of **13a.**



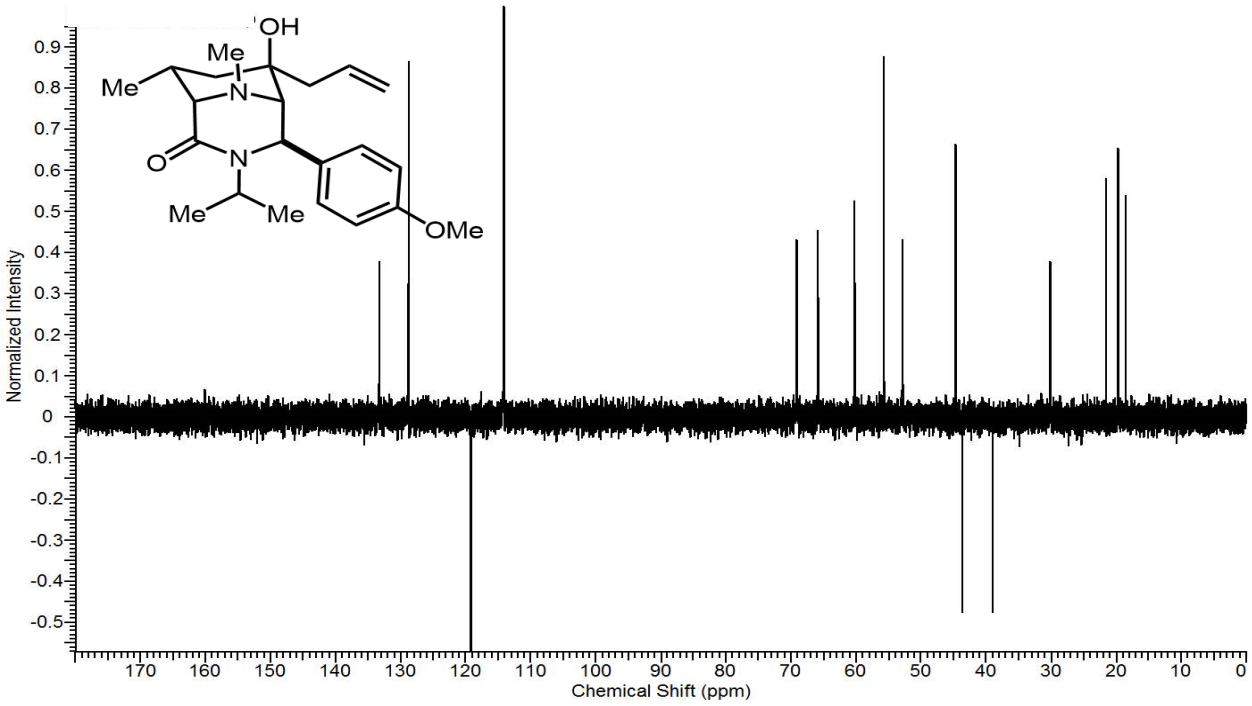
Spectrum 2-29: DEPT-135 NMR spectrum of **13a.**



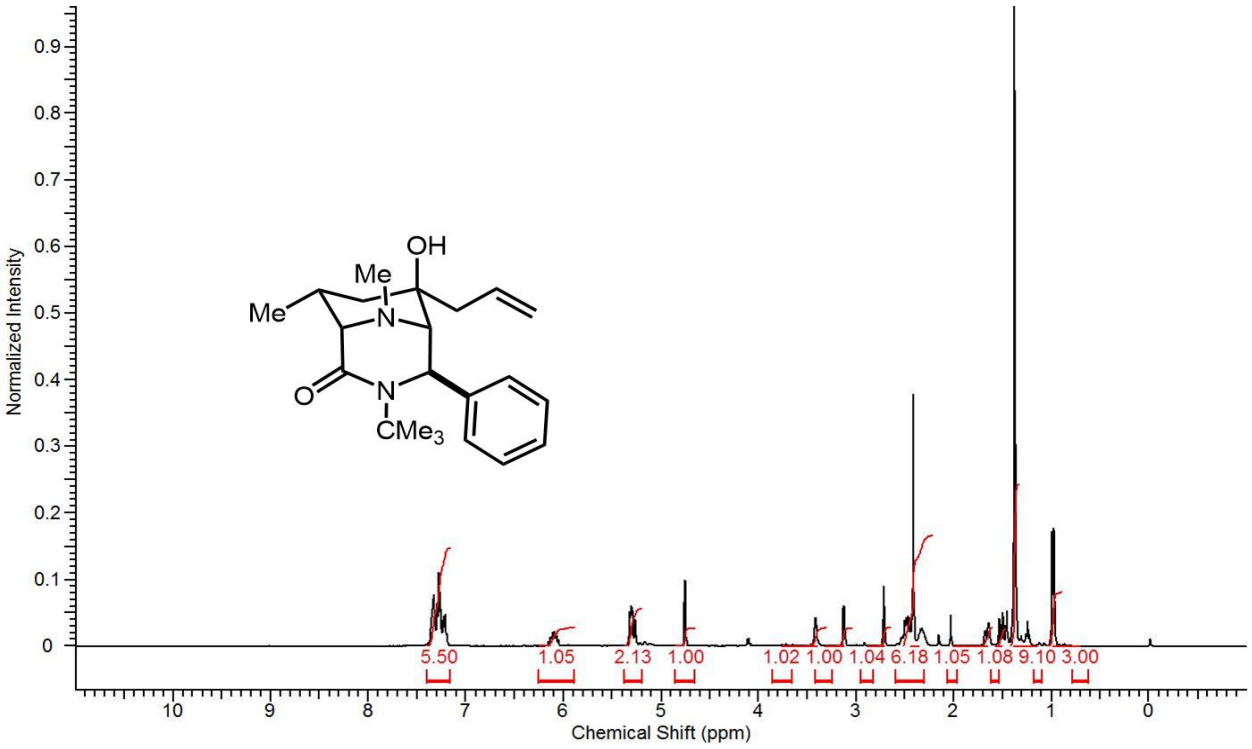
Spectrum 2-30: ^{1}H NMR spectrum of **13b.**



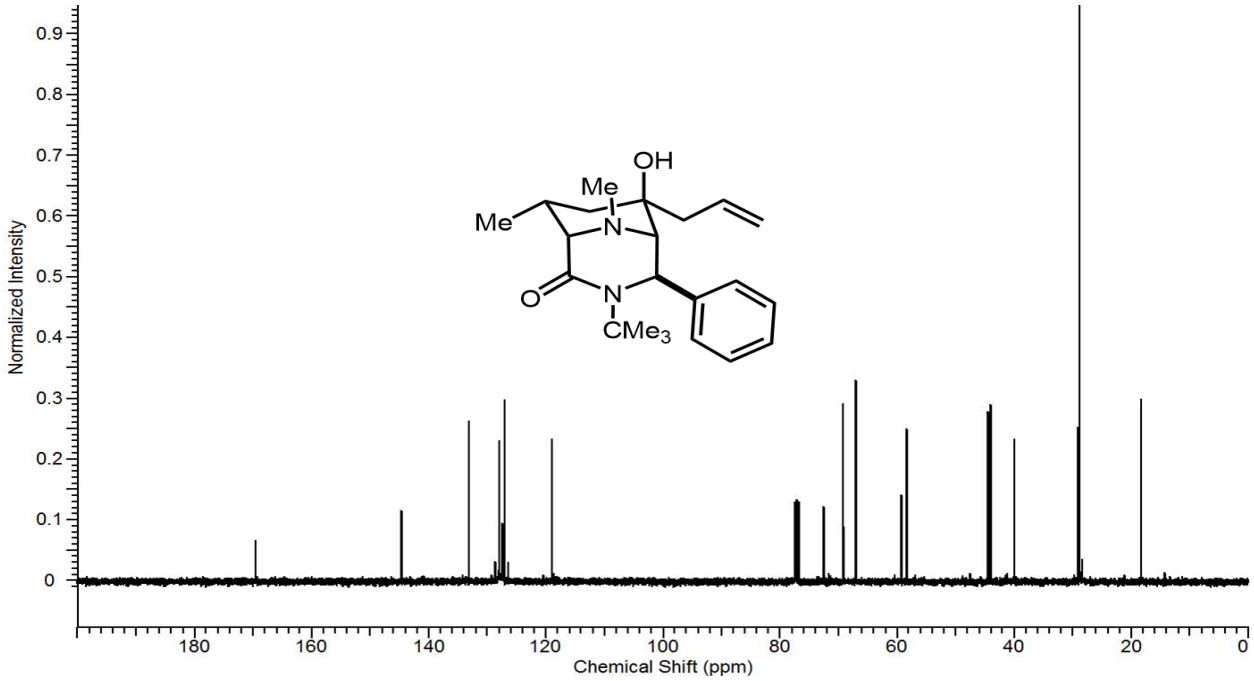
Spectrum 2-31: ^{13}C NMR spectrum of **13b.**



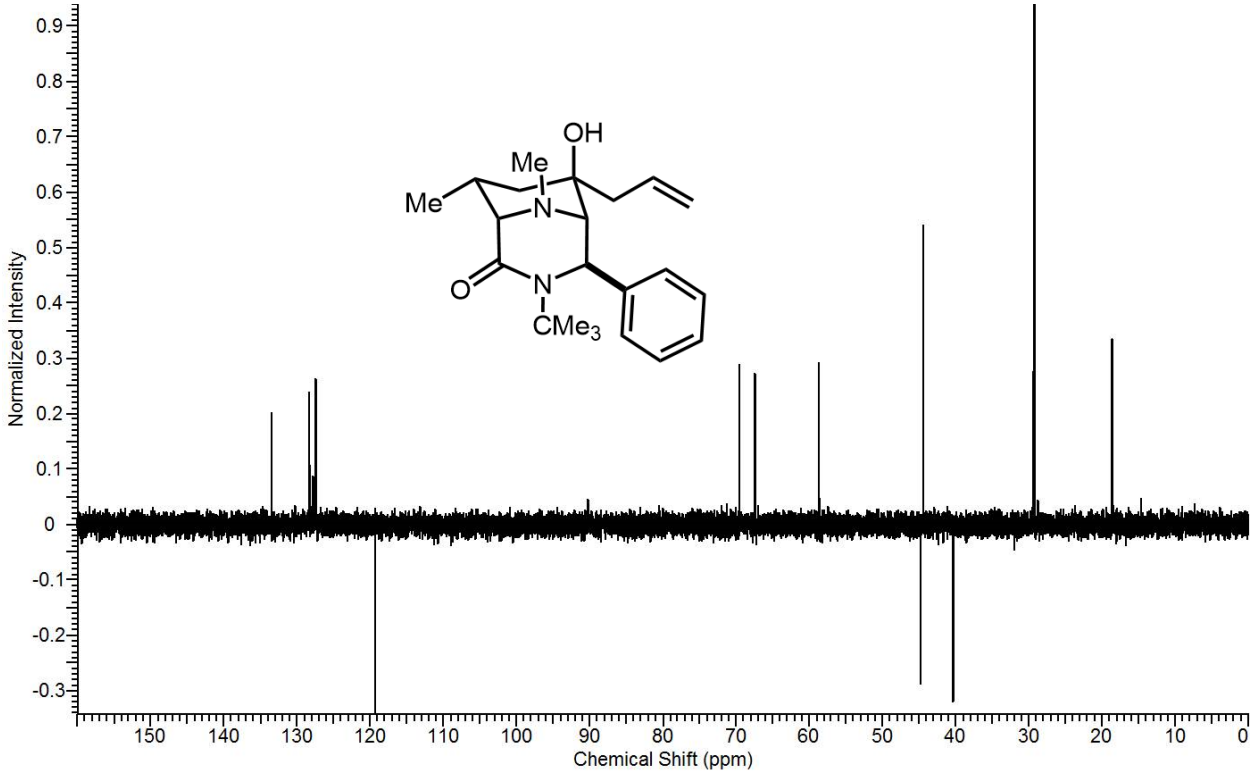
Spectrum 2-32: DEPT-135 NMR spectrum of **13b.**



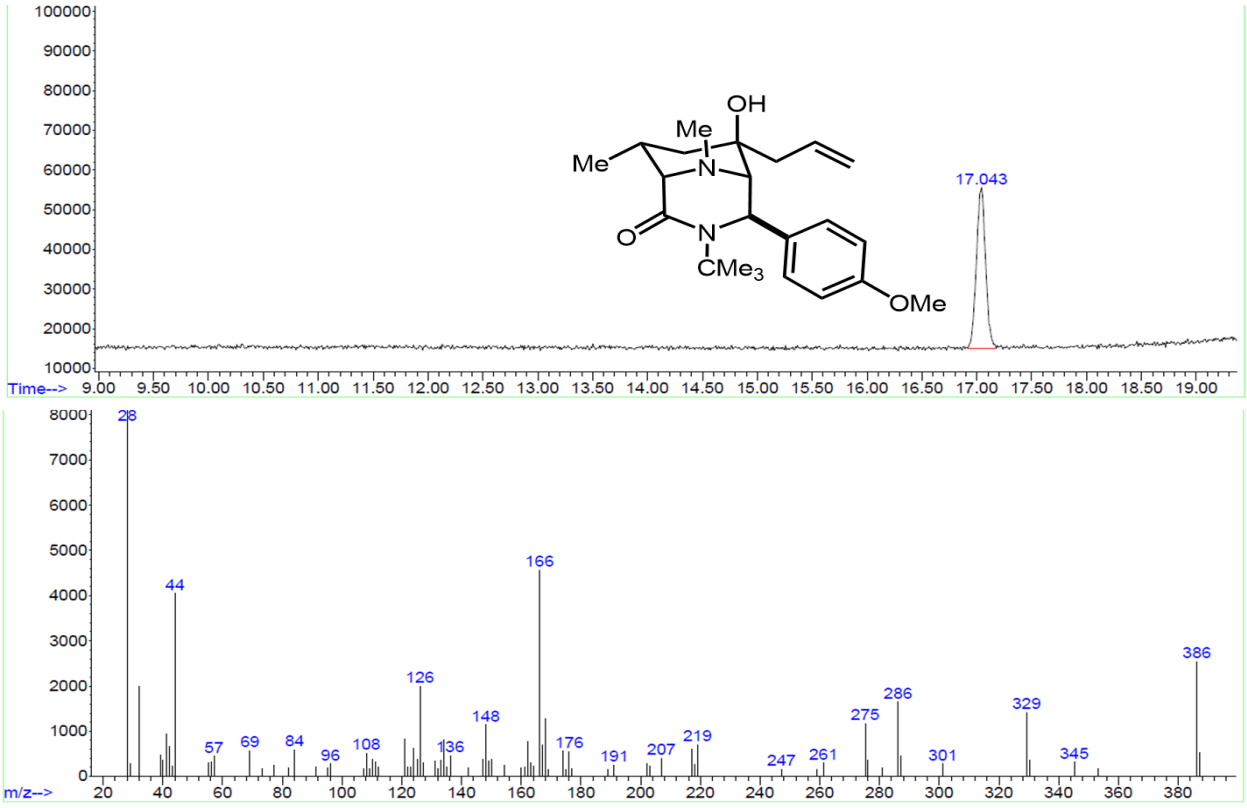
Spectrum 2-33: ^{1}H NMR spectrum of **13c.**



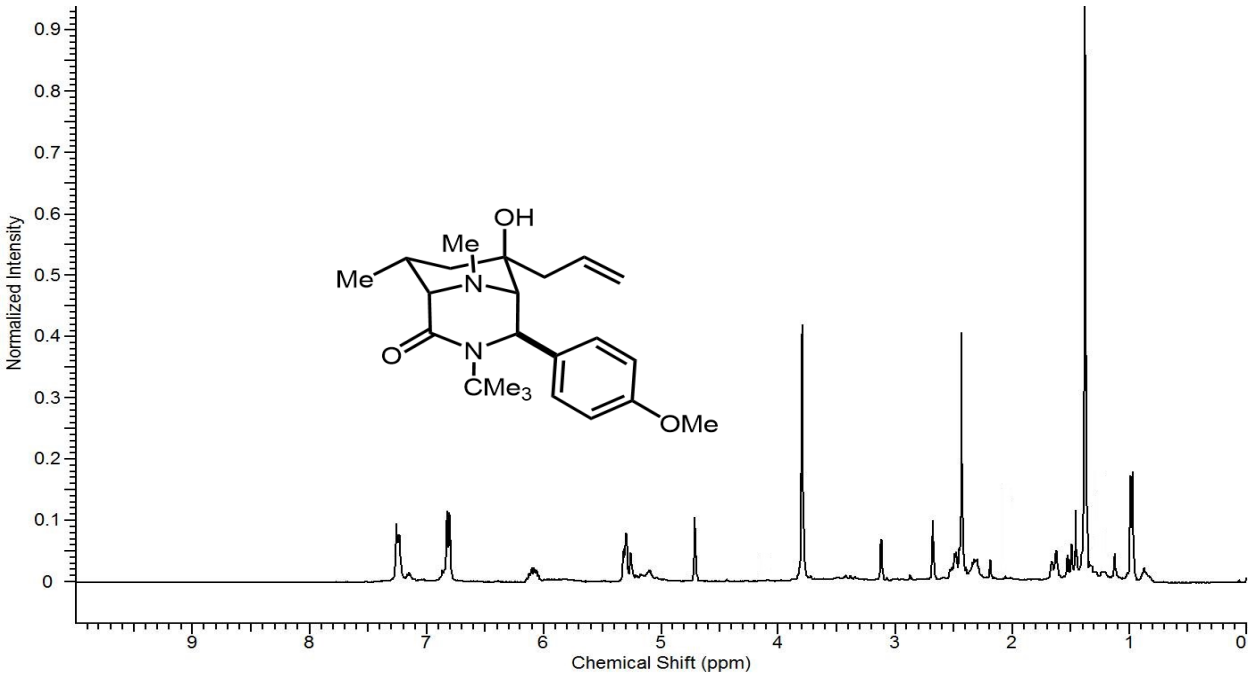
Spectrum 2-34: ^{13}C NMR spectrum of **13c.**



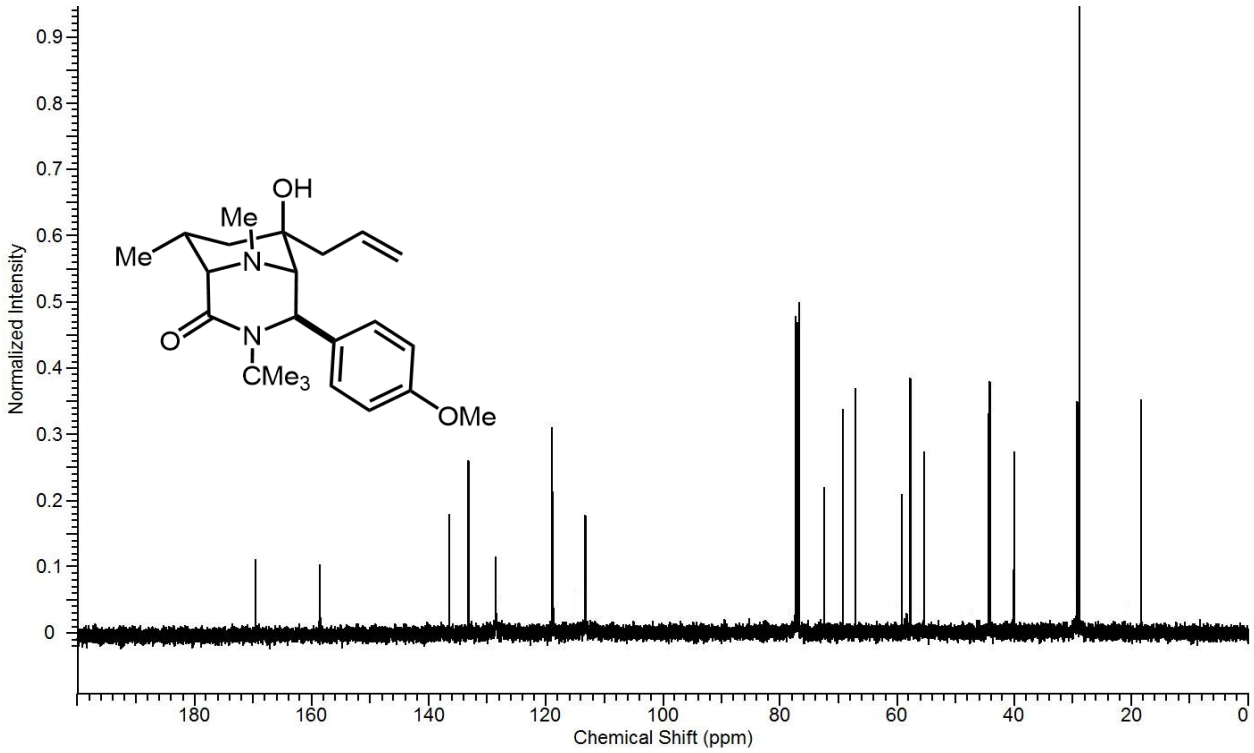
Spectrum 2-35: DEPT-135 NMR spectrum of **13c.**



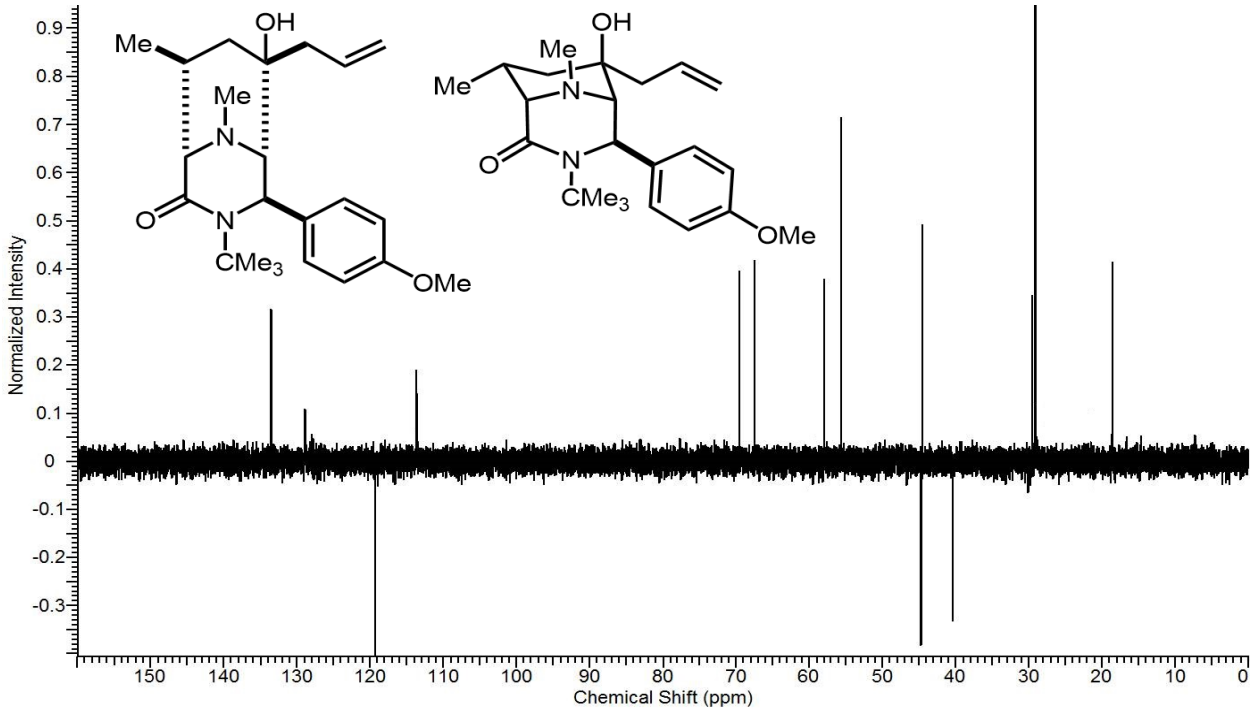
Spectrum 2-37 and 2-38: GC and MS spectra of **13d.**



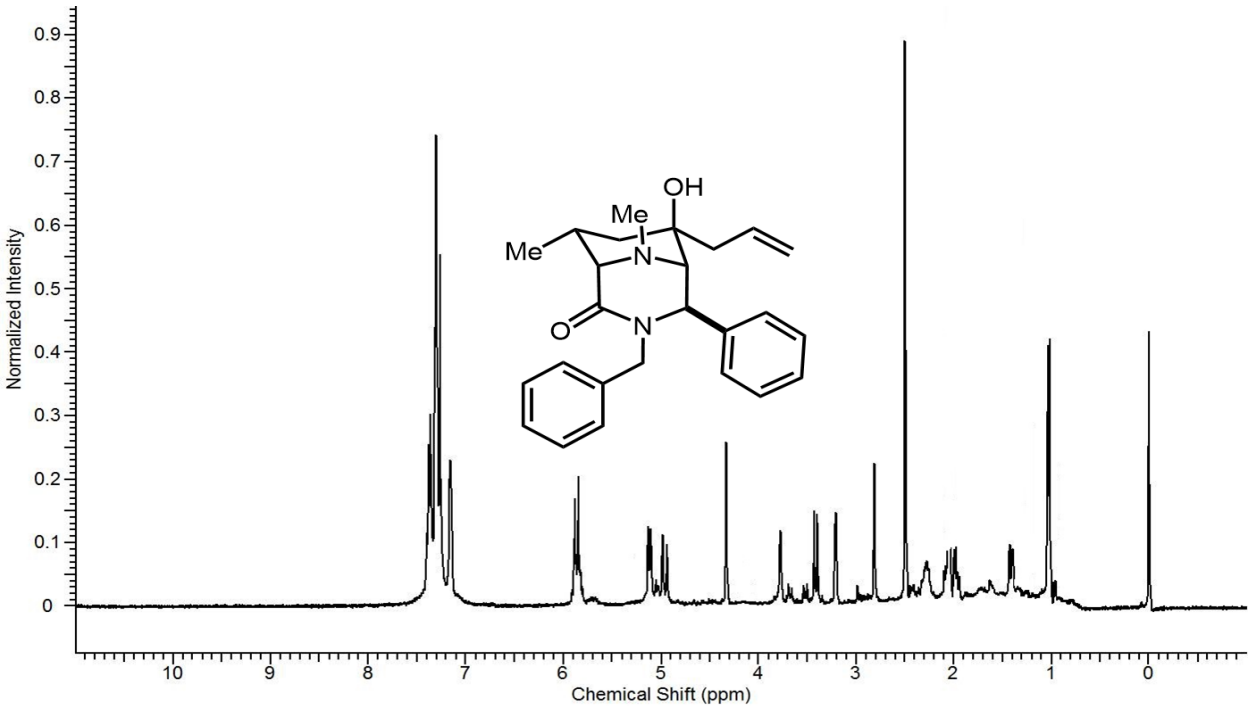
Spectrum 2-39: ^{1}H NMR spectrum of **13d.**



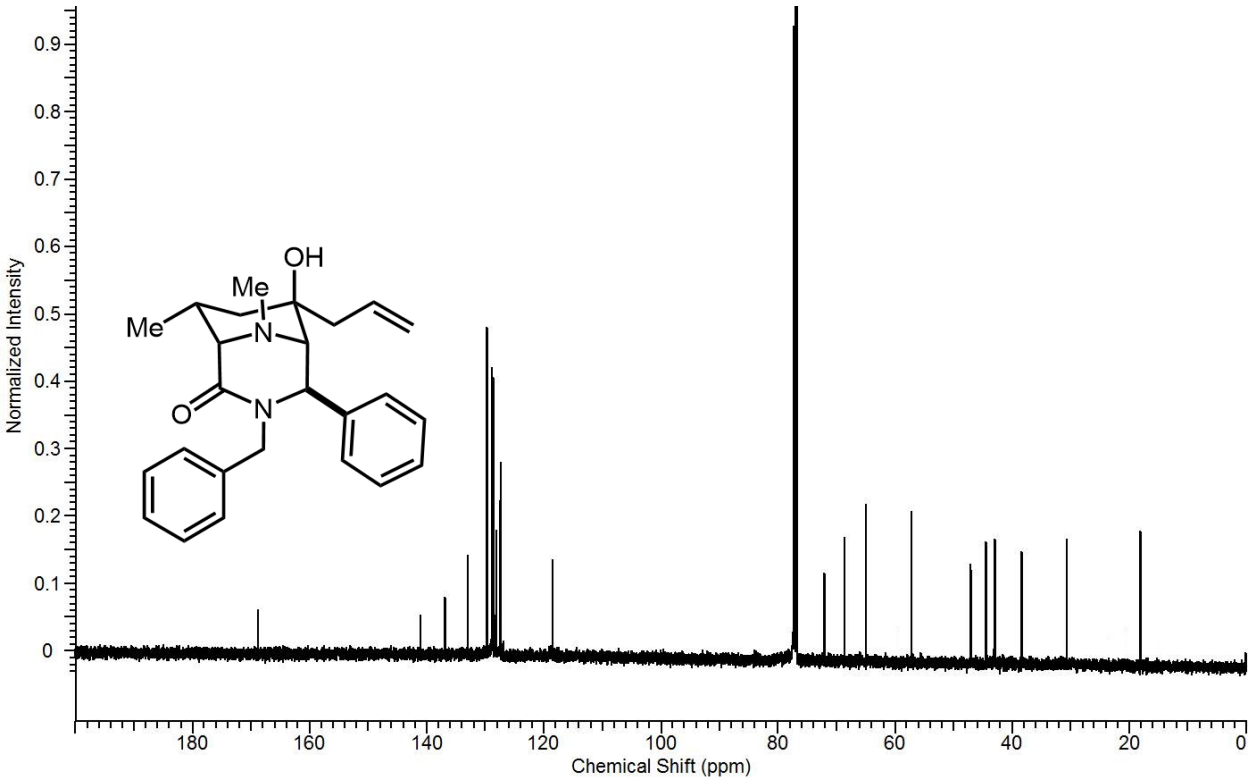
Spectrum 2-40: ^{13}C NMR spectrum of **13d.**



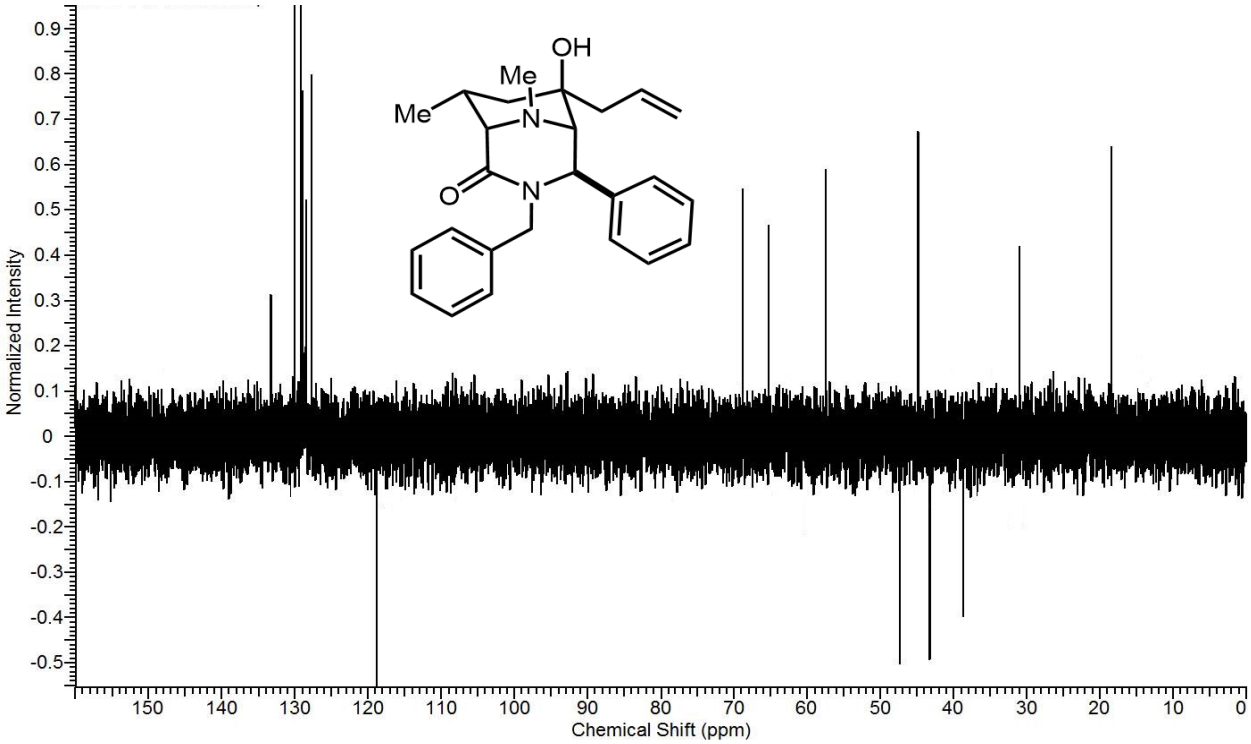
Spectrum 2-41: DEPT-135 NMR spectrum of **13d.**



Spectrum 2-42: ^{1}H NMR spectrum of **13e.**



Spectrum 2-43: ^{13}C NMR spectrum of **13e.**



Spectrum 2-44: DEPT-135 NMR spectrum of **13e.**